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TREATMENT OF ASTHMA WITH CHLORTROPBENZYL

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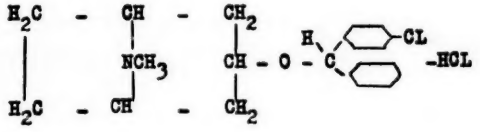
NUMEROUS preparations have been employed in the treatment of asthma, namely the sympathomimetics, the antihistaminics, and the steroids. Despite the use of such drugs as atropine, benadryl, and prednisolone, the control of asthma still presents a problem, foreboding in many of its aspects. Because this disease can often assume such a crucial status, the trials of new and better methods of therapy and prevention are indicated. This presentation deals with the trial and successful use of a new agent, fairly unique in its attributes.

Chemistry.—Chlortropbenzyl has the following chemical structure:



Basically, this agent is composed of two moieties—a tropine nucleus and a benzhydryl nucleus. The tropine nucleus apparently provides antispasmodic effect in the manner of atropine. The benzhydryl nucleus provides antihistaminic action like Benadryl, its forbear. Chlorination on the benzhydryl ring has apparently altered the action of the entire compound in producing a more potentiated and prolonged action, such as is obtained

Chlortropbenzyl was supplied by Wyeth under the name of WY 2149 and by Schenley under the name of FC 1.

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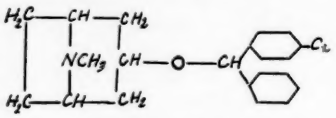
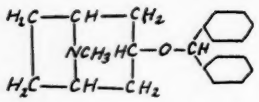
in the chlorination of Trimeton,® producing Chlor-Trimeton.® This chlorination has also altered the compound's activity in other aspects, as will be pointed out later. The drug has strong tranquilizing action based

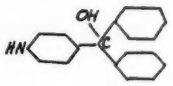
CHLORTROPBENZYL AND RELATED COMPOUNDS



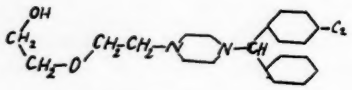
Chlortropbenzyl



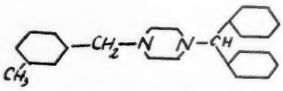
Benztropine (Cogentin)



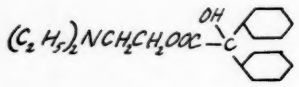
Azacyclonol (Frenquel)



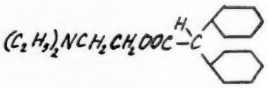
Hydroxyzine (Atarax)



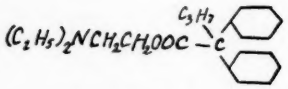
Meclizine (Bonamine)



Benactyzine (Suavitil)



Adiphenine (Trasentine)



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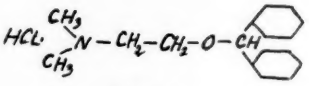
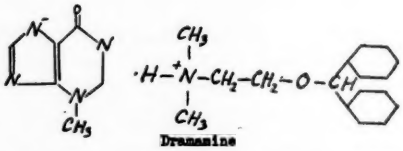


Benadryl

Other related diphenyl methane compounds:

Captadiamine (Suvren)

Vistaril



Dramamine

on the benzhydryl ring. This is similar to other benzhydryl compounds, *i.e.* Suavatil, Frenquel.

The above table shows the similarities of all these related drugs.

Pharmacology.—Various pharmacological studies have been done on this agent by Chen,[1,2] members of Merck Institute,[3] and Wyeth Laboratories.[4] The following is based upon results in these studies.

1. *Toxicity.*—The toxicity of this compound is minimal, with a wide margin of safety. In studies done on mice, the oral LD_{50} was found to be 174±3.4/mg/kg, using 0.5 ml volume solution, administered by gastric tube. Intraperitoneal LD_{50} was 31.7± 1.9 mg/kg. In nine dogs pentobarbitalized, the mean minimal lethal dose was 28 mg/kg. Chronic toxicity studies done in dogs and rats showed this compound to be safe even at very high dosage. In man, the drug has shown no ill effects when given on a continuous basis for over five years.

2. *Antihistaminic Action.—The antihistaminic action of the drug is pronounced and prolonged.* In comparison with other available antihistaminics, it was found to produce the longest effect on the lowest dosage basis. *In guinea pigs exposed to histamine spray, an effect was produced for as long as seven days.* The best that could be provided by another antihistaminic, Chlorprophenpyridamine (Chlor-trimeton®), was one day. In studies done on dogs demonstrating inhibition of histamine-induced vaso-depression, a similar prolonged effect was obtained with Chlortropbenzyl as compared to Chlor-Trimeton® and Pyribenzamine®. Various other experimental studies done with this agent have demonstrated it to be a powerful and prolonged-acting antihistaminic.

3. *Antispasmodic Activity.*—In a study using a modification of Costello and deBeer's method on tracheal rings, results were studied against acetylcholine-induced contractions. Histamine-induced contractions were readily controlled by Chlortropbenzyl, giving 90 per cent relaxation, as compared to 75 per cent for atropine sulfate and 25 per cent for methaniline bromide (Banthine®). (This type of test suggests a high amount of efficacy to be expected in the treatment of asthma.)

4. *Antisialogogue Effect.*—Chlortropbenzyl demonstrated inhibition of pilocarpine-induced salivation only to a small degree when compared with atropine and Banthine.® In this study, the drug was only 21.4 per cent effective in controlling salivary secretion due to pilocarpine; atropine was 83.5 per cent effective, and Banthine® 47.2 per cent. Results indicate that Chlortropbenzyl does not have as great a drying effect on the salivary secretion of animals as do atropine and Banthine®.

5. *Mydriatic Effect.*—Chlortropbenzyl has less mydriatic effect than does atropine sulfate. It has no effect on the pupillary size, when injected intravenously, whereas atropine sulfate does. The mydriatic effect of the drug on topical administration is minimal when compared with atropine and related compounds.

6. *Antiemetic Effect.*—Studies on dogs with apomorphine-induced vomiting indicated that the drug has some action in this category. It compared favorably with Chlorpromazine. Other antihistaminics, such as Chlor-Trimeton® and Pyribenzamine®, have no inhibitory effect of this nature.

7. *Antimorphine Activity.*—When Chlortropbenzyl and morphine were administered to mice, the Straub-tail reaction of circular movement of these morphinized mice was prevented by Chlortropbenzyl. The drug was found to be more active in this sphere of activity than was atropine sulfate.

8. *Central Nervous System Effects.*—The effects of Chlortropbenzyl were studied in a number of ways. It was demonstrated that the catatonia-like state induced

by the intraperitoneal injection of prochlorperazine was prevented, the drug was shown to be as effective or more effective than Cogentin® in decreasing the duration of the prochlorperazine catatonia-like state in mice.

An encephalogram study of cats showed that the administration of Chlortropbenzyl tends to reduce the frequency and increase the amplitude of cortical waves. Large, slow waves were produced with the administration of Chlortropbenzyl; these waves were noted to be similar to a sleep pattern.

9. *Anesthetic.*—In addition to the above cited attributes of Chlortropbenzyl it also is a local anesthetic.

CLINICAL STUDIES

In addition to the published papers on pharmacology by James Y. P. Chen[1,2] two other papers concerned with clinical studies with Chlortropbenzyl have been published. The first, by Kaplan *et al.*,[5] entitled "Clinical Evaluation of a New Antihistamine Drug, FC-1," described the use of this agent in 160 patients suffering from ragweed pollinosis who received 2.5 to 15 mg daily. Effectiveness was noted in fifteen to thirty minutes, and lasted up to twelve hours.

In a paper titled "Observations of the Clinical Trial of Tropin-4-chlorobenzhydryl Ether Hydrochloride," by Dutton and Halpin,[6] a report was made of a group of ninety-nine patients who were treated for allergic conditions: "Prolonged relief (eight to twelve hours) was noted by several patients, and good response was observed . . . for as long as twelve to twenty-four hours . . . FC-1 appeared to possess the following advantages; infrequent administration, prolonged satisfactory relief, and relatively few serious side-effects on a low dosage program."

The drug was employed in a series of thirty asthmatic patients, in a dosage ranging from 2.5 mg to 10 mg per day. The drug was supplied as a 5 mg scored tablet. The patients consisted of eighteen men and twelve women ranging from three to sixty-eight years of age. Most of the patients took the drug as a 5 mg tablet approximately one hour before bedtime. With this mode of administration, patients noted that they obtained an excellent night's sleep and were not drowsy the following day. Only very infrequently were complaints of drowsiness and lightheadedness noted. Some of the patients noted dryness which was tolerated later to the degree that they did not complain further. During the course of therapy, all of the patients received the drug alone, except for some vitamin therapy. No desensitization therapy was given to these patients. It was noted that the drug was effective in maintaining these patients almost completely symptom-free as long as they remained on therapy.

Evaluation of the beneficial results obtained in each case was determined on the basis of the patient's status prior to therapy. In a few cases, the patients were placed on a similar drug for a short period of time, for comparative purposes. Each patient was graded on a one to four plus scale according to benefit received. The number in each category was as follows:

	None	Slight	Fair	Good	Excellent
Benefit received	0	1+	2+	3+	4+
Number of patients	0	1	5	10	14

It was noted that good to excellent benefit was more consistently obtained in the younger patients. Apparently some of the older patients had a good deal of emphysema complicating their asthma, and this could not be resolved. The asthma component in these elderly people was well-resolved, however, since they had practically no "attacks" while on therapy. The one patient who was graded as "one plus" benefit was over sixty-five years of age and had bronchiectasis as well as emphysema and intrinsic asthma. He did well but was limited in his improvement by these complications. His case was the one exception where supplementary therapy was given along with Chlortropbenzyl.

The side effects with this agent were negligible. These consisted of blurring of vision, drowsiness, and dryness of the mouth. In only two of the patients were these effects pronounced. After alteration of dosage, reduction to 2.5 mg taken nightly, they continued on the treatment without further difficulty. One patient on initiation of therapy took two tablets (10 mg) instead of one and was apparently very sensitive to Chlortropbenzyl's effect. He indicated that he was sleepy for the next day and a half. With reduction in dosage to 2.5 mg nightly, he had no difficulty. In the following case histories it is noted that a patient who on rare occasions took 15 mg (three tablets) daily experienced no difficulty.

The following three cases are presented to demonstrate the typical results obtained.

Case 1.—The patient, a white man, twenty-nine years of age, had suffered from asthma since the age of fifteen. During his long course of therapy, he had received all forms of treatment, including desensitization, antihistaminics, inhalation therapy, and various other types of therapy. Up until the time of initiation of treatment, he was self-administering Isuprel inhalation as often as twenty-five times a day. On July 24, 1956, therapy with one to three tablets of Chlortropbenzyl daily was instituted. The patient obtained immediate relief of symptoms, without experiencing any side effects, although he had taken as much as 15 mg of the drug daily. From 1956, to the present, he has remained on this therapy continuously except for one occasion when he was without medication for about five days. At that time, he again began to experience asthmatic attacks. Since he has resumed therapy, he has had no further attacks.

Blood counts, urinalyses, x-rays and electrocardiographs have been done on a yearly basis on this patient. At no time was any abnormal result obtained.

Case 2.—The patient, a twenty-two year old white woman, suffered severe asthmatic attacks. Therapy was initiated in January, 1953, and has continued on an intermittent basis since that time. The patient has taken one or two tablets of Chlortropbenzyl daily, usually one in the evening and one in the morning. No further asthmatic attacks occurred until she lapsed treatment. Her asthma recurred so acutely that hospitalization was necessary. Steroid therapy was

used to control her acute condition. Chlortropbenzyl therapy was resumed upon her discharge from the hospital and was maintained until 1955, when bronchopneumonia necessitated rehospitalization. Since 1955, the patient has maintained herself quite well with Chlortropbenzyl, but occasionally neglects taking her medication. When this occurs, she is usually troubled with asthma. Various laboratory tests have been done on the patient during the last five years, including blood counts and liver studies. At no time was any alteration noted that could be ascribed to the medication. No side effects were noted at any time, nor has the patient complained of any untoward effects.

Case 3.—The patient, a seven and one-half year old boy, has been under Chlortropbenzyl therapy from September 21, 1957, to the present. Both parents have strong allergic backgrounds. His own allergic history goes back to infancy. Prior to treatment, he experienced asthmatic attacks two to three times a week and even more frequently when he had the slightest upper respiratory infection. The child's mother was in a chronic anxiety state because of the severity of his condition.

The patient has received from one to two 5 mg tablets daily, except for a short period of one and one-half months in the summer of 1958, when he was without treatment. Soon after initiation of therapy, the child showed great improvement. In the first two months of therapy, he gained six pounds and had no asthmatic attacks. While taking one to one and one-half tablets daily, he was much easier to get along with and had almost no upper respiratory tract infections, as he so frequently had in the past. The patient lapsed treatment in the summer of 1958. In October, he experienced an asthmatic attack. Since the resumption of therapy, the patient has remained free of symptoms. On October 25, 1958, his weight as compared to a year before was eleven pounds greater, and his height had increased by two and one-half inches. This unique effect is significant since prior to therapy his weight and height were slightly below normal, and after one year both were above normal. Blood counts and urinalyses done at various times during the year were all fairly normal except for eosinophilia, ascribable to his allergic status. In conclusion, the asthmatic condition of this patient was completely relieved for twenty months by the administration of Chlortropbenzyl. The only attack suffered during this period was after a lapse of therapy.

In sixteen of the thirty patients, therapy was administered intermittently, since these patients were bothered by their asthma only on occasion. These patients came back and resumed therapy as they found it necessary. In the remaining fourteen patients, therapy was for the most part on a continuous basis. Improvement was noted in all the patients. The drug was not found to be effective in alleviating the acute attack, as would epinephrine, but it was very effective in preventing further attacks.

Many of the patients noted the tranquilizing effect to be quite pronounced. Some commented that they could face their problems with greater ease while on this medication. In two cases, patients who had food allergy as well as asthma, were able to violate their strict diet and enjoy foods previously forbidden them.

The three children included in the study were three, five, and seven and one-half years of age when therapy was begun. They tolerated much larger doses on a dosage for weight basis. The dosage range was from 2.5 to 10.0 mg. daily. They gained weight at a rate higher than they ever

did before (Case 3). The drug may have anabolic effect, or it is the tranquilizer action that is responsible for the improvement in weight gain. No effect was noted on the children as regards sedation, eye signs, or dryness of the mucous membranes.

SUMMARY

Studies on a new antispasmodic, antihistaminic, tranquilizer drug are presented in which very promising results are reported in the treatment of asthma. Thirty patients from three to sixty-eight years of age were treated with Chlortropbenzyl for periods up to five years. The drug was administered in 5 mg tablet form in doses ranging from 2.5 to 15 mg daily. This drug was found to be effective in preventing asthmatic attacks in the thirty patients undergoing therapy. Side effects were minimal. It is felt that Chlortropbenzyl is a valuable adjunct in the treatment of asthma.

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Submitted July 15, 1959

SAFE AT HOME?

In the twenty-two months ending in April 1958 about 600,000 American children are estimated to have been poisoned through the ingestion of toxic chemicals found in or close to the ordinary American home; how many more cases of poisoning occurred but were not recognized will never be known, but the number is probably not negligible. About 500 of the children died of poisoning. Accidental poisoning is essentially a pediatric problem; its incidence in adults is only about a tenth of its frequency in children. Among the children poisoned nearly all were under five years of age, the largest number being between one and two.

Aspirin, usually in the candied form, accounted for 25 per cent of the total number of cases of poisoning in children. The other commonly encountered toxins were bleaches, detergents, soaps, water-softeners, waxes and polishes, lighter fluids, insecticides and herbicides, and cosmetics.—Editorial, *Medical Science*, 5:691-692 (May 25) 1959.

ASTHMA SECONDARY TO CARDIOSPASM

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Cardiospasm as a cause of respiratory symptoms has received scant attention in the literature on allergy, although esophagoscopists have long been aware of this relationship. Plummer and Vinson[1] first called attention to it in 1921, and in 1924 Vinson [2] reported that forty-nine (11 per cent) of 415 patients with cardiospasm had nocturnal cough and dyspnea after meals. Andersen, Holman and one of us[3] (A.M.O.) in 1953 reviewed 601 cases of cardiospasm and found that in 131 (21 per cent) the patient had respiratory symptoms or findings. A significant pulmonary complication was demonstrated in sixty-three patients: forty-six had aspiration pneumonitis, five had bronchiectasis, five had tuberculosis or suspected tuberculosis, two had emphysema and one had pulmonary abscess. An appreciable but unrecorded percentage showed mediastinal widening due to enlargement of the esophagus. The remaining sixty-eight of the 131 patients complained of cough but had no demonstrable pulmonary disease. Several patients stated that their cough was paroxysmal and often crowing in type. Typical asthmatic attacks occurred in four patients. Three of these were in the group showing pneumonitis, but the thoracic roentgenogram of the fourth patient did not show evidence of any abnormality.

Moersch[4] pointed out in 1929 that cardiospasm, especially in children, might go unrecognized, mistaken for croup, chronic respiratory disease, or even a feeding problem. In 1936 Schmidt[5] reported typical asthmatic symptoms in a six-year-old girl whose roentgenogram showed widening of the upper portion of the mediastinum. Marked dilatation of the esophagus was demonstrated by a barium swallow, and forceful dilatation of the cardia relieved the asthma completely.

The following case is typical of persons manifesting asthma with cardiospasm.

REPORT OF CASE

A thirty-six-year-old man came to the Mayo Clinic because of cough, wheezing and exertional dyspnea of increasing severity over a seven-year period. He had never been aware of any definite precipitating factor, but was usually worse at night. He had experienced occasional febrile attacks accompanied by mild cough and dark sputum. There were also mild symptoms of perennial rhinitis and nasal stuffiness. During the prior four years he had been aware of lower substernal fullness after meals; rarely he regurgitated a small bolus of food.

According to the patient a roentgenogram made two years previous to his admission had shown upper mediastinal widening which was thought to be due to lym-

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phadenopathy. A year of desensitization treatment after skin tests had been without effect, and an elimination diet had been of only questionable value. Ephedrine compounds had provided partial, transient relief. In a program of avoiding animal

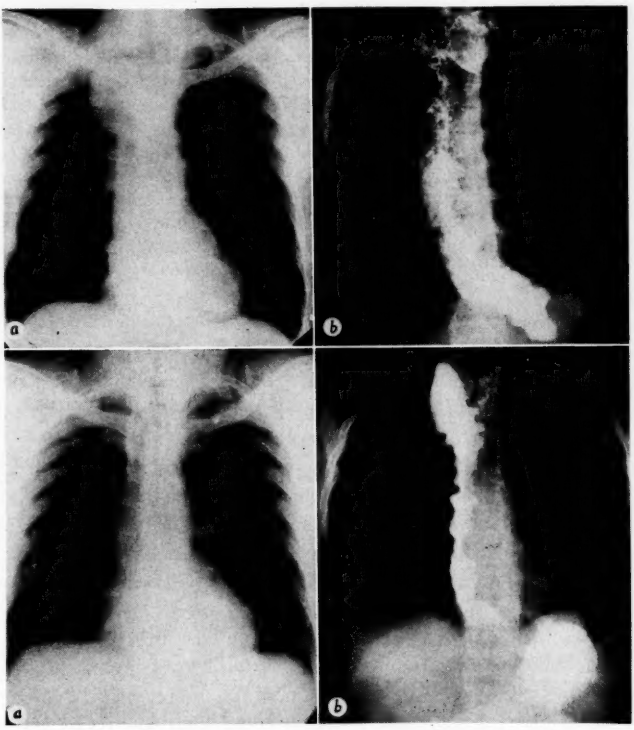

Fig. 1. *(above)* Cardiospasm, before treatment. *(a)* Roentgenogram of chest shows widened mediastinum with probable fluid level. Lung fields negative. *(b)* Roentgenogram of esophagus shows enlargement and tortuosity with no passage of barium into stomach.

Fig. 2 *(below)* Cardiospasm, five months after surgical treatment. *(a)* Roentgenogram of chest shows recession of mediastinal widening. Lung fields negative. *(b)* Roentgenogram of esophagus shows less dilatation and satisfactory emptying.

danders and grain dusts, the patient had sold his farm and had gone into a small retail business, but the symptoms continued.

At examination, the patient was coughing and was slightly dyspneic on moving around the room. Rhonchi were present throughout both lung fields. There were no palpably enlarged lymph nodes.

A thoracic roentgenogram (Fig. 1a) showed a right superior mediastinal mass which appeared to contain a fluid level. A roentgenogram made after swallowing barium (Fig. 1b) showed marked elongation and widening of the esophagus and an unusually low esophagogastric junction. No material could be seen to enter the stomach even after thirty minutes. The diagnosis was severe cardiospasm, a condition more recently designated as "achalasia." It seemed likely that the patient's

respiratory symptoms were caused by aspiration of material spilling over from an engorged esophagus.

We felt that treatment by dilatation of the cardia would not be successful because of the extreme dilatation, tortuosity and elongation of the esophagus. Consequently, an esophagomyotomy of the Heller type was performed by transabdominal approach. The esophagus was noted to be greatly dilated and the wall thickened. A longitudinal incision was made over the lower two and one half to three inches of the esophagus and it was extended across the esophagogastric junction onto the stomach for about 2 cm. The lumen was not entered and at the conclusion of the procedure the mucosa bulged freely.

Within forty-eight hours after operation cough and wheezing disappeared, and the patient was still free of symptoms when last seen five months after operation. His exertional tolerance returned to normal, and tests of pulmonary function at the time of his last visit showed normal vital capacity with no expiratory slowing. Roentgenograms at that time showed some recession of the mediastinal widening (Fig. 2a), less dilatation of the esophagus, and satisfactory emptying into the stomach (Fig. 2b).

COMMENT

The term "cardiospasm" is gradually being replaced by "achalasia," which simply means failure of the cardia to open. It has been demonstrated that the obstruction is not caused by spasm.[6] In achalasia there is degeneration of Auerbach's plexus in the wall of the esophagus.[6,7] This disturbance is responsible for loss of peristalsis, and esophageal content is not propelled through the cardia. The atonic esophagus tends to become more and more distended. A more exact designation of the entire condition would be "motor failure of the esophagus with achalasia." Esophageal motility studies have confirmed this concept.[8] The cause of achalasia, however, is not known.

The mechanical basis for respiratory symptoms in these cases seems quite clear. With many patients showing a fluid level high in the dilated esophagus, it is easy to visualize this material recurrently spilling over into the respiratory tract, causing persistent irritation. It is also conceivable that the enlarged esophagus exerts pressure on the trachea and bronchial tree, causing additional stimulation to cough. Our patient probably was predisposed to asthma, as suggested by the vasomotor rhinitis. If he had not been so inclined, he likely would have had only bronchitis. Relief of esophageal obstruction simply removed the major source of his irritation, just as in certain other cases of asthmatic bronchitis the discontinuation of smoking or of overcough may effect relief.

The fact that pulmonary symptoms may so greatly overshadow the digestive symptoms means that the allergist occasionally will see such patients at a time when the underlying achalasia is still unsuspected. Fortunately, the presence or absence of this condition can usually be more easily determined than some of the other diseases which must be considered in differential diagnosis.

Certain features of the history should be suggestive. These include respiratory symptoms not correlating well with exposure to any of the usual allergens or respiratory irritants, postprandial regurgitation, in-

creased distress in the recumbent position, and food or mucus running out of the mouth or nose at night, as evidenced by soiling of the pillow. A history of one or more attacks of fever and cough suggesting bronchostenosis and mucus-retention syndrome actually may represent episodes of acute aspiration pneumonitis. If suspicion is aroused, careful questioning often will reveal some degree of dysphagia.

Roentgenograms of the thorax may not show any abnormality, but mediastinal widening or pneumonitis compatible with aspiration should arouse suspicion. A roentgenographic study of the esophagus commonly settles the question.

Once a diagnosis of achalasia has been made, the patient can usually be treated satisfactorily.[9] The cardia may be forcibly stretched with the hydrostatic dilator or esophagomyotomy may be performed as was done in this case.

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THE PREFACE OF ANDREAS VESALIUS

"Those engaged in the arts and sciences, Most Gracious Emperor Charles, find many serious obstacles to the exact study and successful application of them. In the first place, no slight inconvenience results from too great separation between branches of study which serve for the perfection of one art. But much worse is the mischievous distribution among different practitioners of the practical applications of the art. This has been carried so far that those who have set before themselves the attainment of an art embrace one part of it to the neglect of the rest, although they are intimately bound up with it and can by no means be separated from it. Such never achieve any notable result; they never attain their goal or succeed in basing their art upon a proper foundation."—ANDREAS VESALIUS, *De Humani Corporis Fabrica Libri Septem,* Basilaea, 1543.

SEEDS AS A SOURCE OF FOOD TESTING MATERIAL

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SKIN TESTING as a diagnostic procedure in food allergy has never enjoyed a good reputation for accuracy. There are many reasons for this, some of which may be insurmountable. One important reason is that many food extracts, prepared by conventional methods, are not potent enough to produce positive skin reactions in clinically allergic patients.[1]

Testing materials made from seeds of certain fruits and vegetables and which are customarily made from the pulp might be expected to be more potent, and therefore more accurate, because of the following:

1. It is a biologically sound proposition that substances common to both seed and pulp are more concentrated in the seeds.

2. There is evidence in the literature showing that there are antigens common to seeds and to other plant parts of parsnip,[3] grape,[4] beet,[5] fava bean,[6] ragweed,[9] and grass.[12]

3. Also, in the case of orange, two papers[7,8] exist which present evidence to the contrary and demonstrate that there is no cross-antigenicity between seed protein and juice protein in guinea pig anaphylaxis or in human passive transfer tests. Paradoxically, in one of the same papers,[8] photographs are provided which show excellent skin reactions to citrus seed protein on patients who have clinical sensitivity to citrus fruits. This last observation strengthens the belief that seeds might be expected to be a good source of food testing material.

4. In addition, extracts made from seeds which are eaten as foods, such as nuts, buckwheat, cottonseed, flaxseed, cereal grains, mustard, et cetera, are known to have a relatively high degree of potency, some of them markedly so.

In this paper, data are presented on five foods: tomato, orange, carrot, apple and lettuce. Of this, tomato is the only one in which the seed is usually eaten.

It is a radical departure from the normal procedure to use testing material derived from seeds which are foreign to the diet. The most serious objection to this proposal is that the seeds might not contain the antigenic components of the portion of the plant used as a food. This would result in failure of the seed extracts to react on patients with known sensitivities.

The accompanying photographs compare scratch tests of seed extracts with commercial preparations and with fresh frozen food. The commercial extracts consisted of two glycerinated liquids and a dry powder obtained from different companies. The material was purchased exclusively for this study and was stored at freezing temperature immedi-

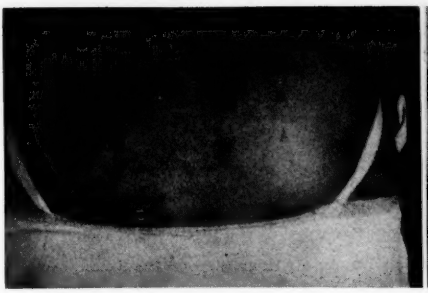

Fig. 1. Patient with asthma from tomato.

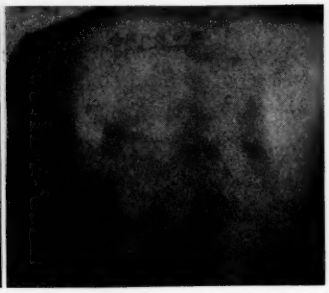

Fig. 2. Patient with nasal allergy from orange.

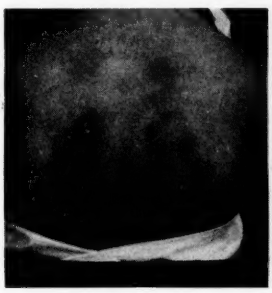

Fig. 3. Patient with nasal allergy and urticaria from carrot.

Fig. 4. Patient with eczema from apple.

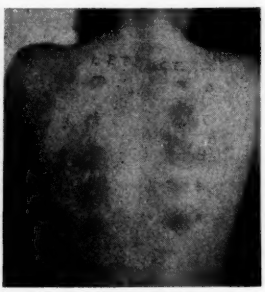

Fig. 5. Patient with asthma from lettuce.

ately on arrival and also between testing procedures. The seed extracts were kept in the same manner. The frozen foods were prepared and handled in the same manner described by Ancona and Schumacher.[2]

In each of the photographs, the same arrangement of the antigens has been followed. There are five tests on either side of the back in vertical rows. Starting from above downward on the left side, the two upper tests are the commercial liquid extracts, that in the center is the seed extract, the next in line is the commercial dry powder, and the last is the fresh frozen food. The same order is followed from below upward on the right side of the back. Each of the patients on whom the tests were made has a clinically proved sensitivity to the food under consideration. The results of the tests, as illustrated in the photographs, make it apparent that the seed extracts compare favorably with the others and in most instances are superior. Thus it is shown that seed extracts will give positive scratch test reactions on patients with clinical sensitivity to the foods being tested.

The next question is whether the seed extracts are irritating to the

skin and therefore unsuitable for general use. Tables I and II summarize the results of routine scratch testing on selected allergic patients. The patients were chosen on the basis of having one of the common atopic diseases (asthma, hay fever, chronic nasal allergy or eczema) and having been followed sufficiently well over a period of time to be reasonably certain that they are or are not allergic to the food in question.

TABLE I. SUMMARY OF RESULTS OF ROUTINE SCRATCH TESTS WITH SEED TESTING MATERIAL ON PATIENTS WITH ALLERGIC DISEASE

Seed Extract	Number of Patients Tested	Negative	Plus-Minus	1+	2+	3+	4+
Tomato	278	208	41	23	5	1	0
Orange	275	205	30	29	6	3	2
Carrot	287	185	50	39	10	3	0
Apple	284	220	27	20	10	6	1
Lettuce	279	205	34	34	5	0	1

It can be seen in Table I that the majority of the skin reactions are negative. Weakly positive, or plus-minus, reactions seemed to have no clinical significance, and these were grouped with the negatives as "negative correct" in Table II. While it is also evident from Table II that a certain number of false positive reactions occurred, there were no false negatives in the groups of patients studied.

TABLE II. ANALYSIS OF DIAGNOSTIC ACCURACY OF SCRATCH TESTS WITH SEED TESTING MATERIAL

Seed Extract	Number of Patients Tested	Negative Correct	False Positive	False Negative	Positive Correct
Tomato	278	249	21	0	8
Orange	275	235	34	0	6
Carrot	287	235	48	0	4
Apple	284	247	34	0	3
Lettuce	279	239	39	0	1

Continued experience in routine testing with seed extracts, involving well over 500 patients, has failed to produce a false negative reaction. Three false negative reactions seemed to occur: to carrot, tomato, and orange. In each instance the sensitivities were already known and the patients had avoided the foods for long periods. When the foods were eaten and the symptoms reproduced, the patients were retested, and each of them then showed positive scratch reactions of one plus or greater. It can then be said that by using seed testing material, false negative scratch reactions in atopic disease have been found to be absent thus far and could at least be expected to be of low incidence. This is a distinct advantage, since it greatly reduces the number of patients who would be suspected of being allergic to a food.

METHOD OF PREPARATION OF SEED EXTRACTS

One observed cause for the low potency of conventional food extracts is that lytic processes can occur at ordinary refrigerator temperatures which may diminish the strength of the extract.[1,11] The use of fresh frozen raw foods as skin testing material has been advocated as a means of circumventing this difficulty.[2] The method of preparation which has been adopted combines the use of seeds and storage at freezing temperatures.

The seeds were readily obtained, either by purchasing them or by retaining them from uncooked fruits and vegetables. To date, the seeds from pear, peach, prune, celery, spinach, grape, cantaloupe, onion, beet, green pepper, watermelon, cucumber, strawberry, cherry, squash, grapefruit, raspberry, cabbage, turnip, and rhubarb, in addition to the five previously mentioned, have been used. The larger seeds were first ground in an ordinary food chopper. The hard external covering was removed from peach, prune, and cherry seeds before grinding, but not from any of the others. Sometimes, considerable oil was released, but the addition of petroleum ether during the grinding process helped to prevent clogging of the food chopper. The ground material thus obtained was further pulverized in a pepper mill, and again petroleum ether facilitated the operation. Smaller seeds were ground directly in the pepper mill. After two or three grindings, a fine powder was obtained which was further defatted with successive washings with petroleum ether to remove as much oil as possible.

The final product was stored as stock material at room temperature under a layer of petroleum ether. Some of this has remained for months without signs of deterioration or apparent loss of potency. When the testing trays were prepared or changed, a small quantity of the stock material was removed, placed on filter paper and the solvent allowed to evaporate. A one ml bottle with an applicator stopper was half filled with dry powder and a mixture of 50 per cent glycerine and 50 per cent buffered saline was added. This made a sort of "mush" of the powdered seed in glycero-saline and this material was used as scatch test material. Time-consuming extracting processes were therefore eliminated. While the potency of the material prepared in this way cannot be determined, it does not seem important, since skin reactions seem to be reproducible after replacement with new material similarly prepared.

In routine use, fresh material was usually withdrawn from stock each month. Between testing, the material was stored in the freezing compartment of the refrigerator. The glycerine, being an anti-freeze, prevented solidification so that thawing was not necessary prior to use. The testing bottles were seldom kept out of the refrigerator freezing compartment for more than a few minutes while in actual use and so had no opportunity to adjust to room temperature for any length of time. Under these condi-

tions, no appreciable loss of potency was observed during periods of up to three months.

Although the possibility has not been thoroughly explored, it seems likely that seeds will yield a stable antigen and that storage in the freezer might not be necessary if the material is extracted and filtered. Since the technique described involves the use of organic material in an aqueous suspension which is frequently subject to possible contamination, storage at low temperature was considered advisable.

Intradermal testing material can also be made from the ground seeds and has proved to be stable, potent, and non-irritating. The method for making the intradermal material is that described by Sheldon, Lovell and Mathews for preparing extracts of cereal grains.[10] The defatted ground material is extracted in 2 per cent weight-volume dilution, in buffered saline. After sterilization by Seitz filtration, the material is ready for use in this concentration.

Intradermal tests were done in most instances as a part of the diagnostic study. While it is felt that the intradermal tests add considerably to the diagnosis when the sensitivities of the patient are unknown, they did not add a great deal to the statistical study done in retrospect. When large positive scratch reactions were obtained, the intradermal tests were not necessary, and were, in fact, contraindicated. When smaller scratch reactions occurred, the intradermal test often pointed strongly to a sensitivity that would perhaps not be regarded as important from the scratch test alone.

SUMMARY

1. Experience with seed extracts indicates that patients allergic to the ingestion of pulp or leaf of certain fruits and vegetables generally give better reactions to crude seed preparations than they do to commercial or fresh frozen material.

2. The chief advantage is that a positive reaction definitely establishes a patient as possibly allergic to the food, while the negative skin reaction makes allergy most unlikely.

3. This does suggest that nature may have provided us with an economical source of concentrated food testing material.

4. A simplified method of preparing testing material is described.

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CHOICE OF TOPICAL CORTICOSTEROID PREPARATIONS

While opinions differ as to the relative effectiveness of the various topical steroids in skin ailments, it is doubtful that any of the newer preparations are clearly superior to hydrocortisone. (Cortisone, as was discovered early in the investigation of corticosteroids, has little if any effect when applied to the skin.) Some investigators consider triamcinolone acetonide to be more effective than other topical steroids, but there are no controlled studies to support this view. Prednisolone, triamcinolone acetonide, fluorometholone, hydrocortamate (or ethamicort), and fludrocortisone are all useful, and the new topical dexamethasone preparations seem to be equally active. Fludrocortisone, unlike the others, is absorbed through the skin in amounts sufficient to cause systemic side effects; therefore it should be used, if at all, with caution, especially near mucous membrane.

Considerably more important than the choice of corticosteroid is the choice of the vehicle in which it is dispensed. In general, acute and subacute eruptions tolerate lotions and water-miscible creams best, while chronic lesions respond better to greasy ointment bases. Aerosols are an expensive and probably ineffective way of administering topical steroids. The majority of patients are best treated with water-washable cream base preparations.

The addition of other medications to the steroid is desirable only where there is a specific indication for both the steroid and the other medication.

Except for fludrocortisone, little or no significant systemic absorption of topical corticosteroids has been noted, even after extensive and prolonged use. A number of observations testify to the marked percutaneous absorption of fludrocortisone, which may be sufficient to cause significant water retention and serum electrolyte imbalance. If this drug is used at all, it should be applied sparingly and only over very small surface areas. The few medical contraindications to any topical steroid therapy are thermal burns, herpes simplex, and varicella.—From the *Medical Letter*, 1:95 (Dec. 11) 1959.

DOMINANT AND RECESSIVE PRECIPITATING AND DESENSITIZING HAPTENS

Introductory Report

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DESENSITIZATION with haptens is one of several aspects of desensitization under investigation in this laboratory. An interesting example of desensitization with haptens was observed during some studies of enzymatic purification of antibody which had been precipitated from Type II antipneumococcal rabbit serum by a hapten, dextran.[1] It is well known that type-specific pneumococcal polysaccharides form precipitates with their corresponding antisera. It is less well known that dextran also forms specific precipitates with Type II antipneumococcal rabbit serum.[2] Examples of dominant antigens have been cited by Burdon[3] in his review of the cellular and humoral theories of anaphylaxis. Cross precipitation between and dominance of homologous over heterologous polysaccharide haptens as adsorbents of precipitin have been demonstrated by Avery, Goebel, and Babers.[4] Against this background the precipitating and desensitizing capacities of dextran and Type II pneumococcal polysaccharide, which precipitate specifically with Type II antipneumococcal rabbit serum, were compared. Two manifestations of the phenomenon of dominant and recessive haptens resulted from this comparison. A description of these experiments and a brief discussion of their significance form the basis of this report.

Experiment I.—A predetermined dose of 10 mg. of dextran in 1.0 ml. of saline was added to 20 ml. of Type II antipneumococcal rabbit serum in 4 aliquots, one daily, of 4.0, 2.0, 2.0 and 2.0 mg. The precipitates were

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Generous supplies of the antiserum, polysaccharide and dextran were donated, respectively, by the Wyeth & Co. Marietta Laboratories, Marietta, Pa., by the Lederle Laboratories, Div. of the American Cyanamid Corp., Pearl River, N. Y., and by Dr. H. M. Tsuchiya and Dr. R. G. Benedict of the Northern Utilization Branch of the U. S. Dept. of Agriculture, Peoria, Ill.

Since this paper was submitted, Heidelberger (The immunological specificity of Type II pneumococcus and its separation into partial specificities II, J. Exper. Med., 111:33, 1960) has shown that a wide variety of hemicelluloses and gums are capable of precipitating Type II antipneumococcal horse serum by virtue of their content of D-Gluclose, L-Rhamnose D-Glucuronic Acid, and 4-Methylglucuronic acid. The first three of these sugars are the principal determinents of pneumococcal Type II specificity. It is quite likely, therefore, that the phenomena reported above can be explained by Heidelberger's data.

removed by centrifugation. The supernatant fluid, after the final addition of dextran, contained an excess of dextran sufficient to precipitate strongly with Type II antiserum.

In similar fashion, Type II pneumococcal polysaccharide was added to another sample of Type II antipneumococcal rabbit serum in 5 aliquots. This supernatant, after separation from the precipitates, contained an excess of polysaccharide sufficient to precipitate strongly with Type II antiserum.

The supernatant which contained an excess of dextran formed a dense precipitate when Type II polysaccharide was added to it. The supernatant which contained an excess of polysaccharide did not form a precipitate when dextran was added.

Since the polysaccharide precipitated all of the specific precipitin for both haptens but dextran precipitated only the anti-dextran precipitin, the polysaccharide is assumed to be the dominant and dextran the recessive precipitating hapten.

Experiment II.—Four guinea pigs were passively sensitized with 0.2 ml. of Type II antiserum intraperitoneally. The next day they were desensitized by giving 5.0 to 8.6 mg. of dextran in five to six intraperitoneal increments. They were challenged several hours after the last injection with 5.0 mg. of dextran, intravenously, as a test of desensitization. There were no reactions. The next day they were challenged with 0.2 mg. of Type II pneumococcal polysaccharide. Two of them died promptly. One nearly died, and one had a moderate anaphylactic reaction. In other words, dextran desensitized actively against dextran but not against the polysaccharide.

Four other pigs were sensitized in the same way. They were desensitized the next day with 2.05 to 2.10 mg. of Type II polysaccharide, given in three intraperitoneal increments. The next morning they were challenged with 0.1 mg. of Type II polysaccharide, intravenously, as a test of desensitization. They did not react. One hour later they were challenged with 5.0 mg. of dextran. They did not react. These animals were desensitized by the polysaccharide against both the polysaccharide and the dextran.

As controls, two sensitized pigs were challenged intravenously with 0.1 mg. of polysaccharide and two with 2.0 mg. of dextran. All four of the animals died in acute anaphylactic shock.

The obvious interpretation is that the polysaccharide is the dominant and dextran is the recessive desensitizing hapten, since the polysaccharide desensitized against both of the haptens whereas the dextran desensitized only against itself.

COMMENT

The pneumococcal polysaccharide and the dextran are referred to as haptens because in this laboratory they have failed repeatedly to immunize

rabbits and to sensitize guinea pigs, although they precipitated strongly with Type II antiserum and elicited anaphylactic shock in sensitized guinea pigs. In another experiment,[1] precipitin which had been precipitated from Type II antipneumococcal serum with dextran, purified with dextranase, reprecipitated and repurified twice, still precipitated with both dextran and Type II polysaccharide, and mediated the same dominant and recessive precipitating hapten phenomenon outlined in Experiment I.

The polysaccharide is referred to as the dominant hapten because it removed the anti-dextran and the anti-polysaccharide precipitin and desensitized the guinea pigs against both haptens. Dextran is described as the recessive hapten because it removed only the anti-dextran precipitins and desensitized only against dextran. The terms dominant and recessive haptens have no genetic implications here. They were used because they seemed more descriptive of these experiments than older terms such as "major and minor antigens," "heterologous and homologous haptens" or "reciprocal cross and unilateral neutralization" which have been used in related but not identical experiments.

Immunological relationships such as those described here could have been anticipated from the literature. For example, Avery, Goebel and Babers[4] demonstrated cross precipitation and the dominance of homologous over heterologous haptens in precipitin absorption experiments, using *alpha* and *beta* glucosides and their protein conjugates. It would seem that they had something similar to these experiments in mind when they wrote: "In view of these findings it seems not unlikely that in the case of the polysaccharides, because of their more complicated structure and greater possibility for variation in molecular configuration, there may be found many examples of a similar overlapping specificity among carbohydrates of unrelated origin." Landsteiner and his associates,[5-a,b,c] using simple chemical compounds conjugated to proteins as experimental models, contributed greatly to the formulation of the principles which govern cross reactions between haptens and "specific" antibodies. Of particular interest is their comment:[5-a] "Precipitin reactions with antigen with binding groups of known chemical structure leave no doubt that a single precipitin will react regularly with other substances if their chemical structure is sufficiently near to that of the homologous antigen. . . . The affinity of antibodies for natural antigens is not absolutely restricted to a single substance but can extend to other similar ones."

Sherman and Stull[6] used the term reciprocal cross neutralization to describe the experiments in human skin in which the addition of one allergen, to certain but not all multivalent reaginic sera, neutralized the reagin of another closely related allergen, *e.g.*, cat versus dog, or horse versus cow. They used the term unilateral neutralization when a strongly reacting allergen-reagin mixture prevented the subsequent reaction with a weaker allergen. The reaction of the weaker allergen-reagin mixture did not prevent a subsequent reaction when the stronger allergen was used.

Maunsell[7] reported somewhat similar results in paired skin sites in allergic patients partially desensitized by repeated injections of different allergens. In other words, when allergens A and B reacted equally in adjacent skin sites, desensitization of those sites by their respective antigens desensitized both sites against both A and B allergens. But when allergen B elicited a weaker initial reaction than allergen A, desensitization of site B desensitized against allergen B only, while desensitization against A desensitized against both A and B. Nicoll and Campbell[8] claimed that strips of ileum from guinea pigs which were sensitive to two antigens of different potency would react poorly to the weaker antigen after reacting maximally to the stronger one. But the reverse was not true. They suggested that their observations should be repeated with better controls. Dale and Hartley[9] used the term "cross desensitization" to describe the partial or complete desensitization of uterine horns against horse albumin, euglobulin, and pseudoglobulin by desensitizing with either antigen. It is of course quite likely that, in 1916, each of their three desensitizing proteins contained enough of the other two to explain their results by specific rather than by cross desensitization.

None of the above observations are entirely comparable to the experiments reported here. The precipitin absorptions in experiment I are similar to those of Avery, Goebel and Babers,[4] but differ in that the immunological relationship of dextran and pneumococcal polysaccharide haptens, synthesized by unrelated micro-organisms in widely divergent forms, is purely fortuitous. Although the dominant and recessive hapten desensitization phenomenon outlined in experiment II is a logical sequel to experiment I, no comparable experiment has been found in the literature.

The observations reported here raise, but do not settle, the question of whether the individual antibody molecules involved were capable of reacting with both haptens or whether separate molecules were needed. Persistence of the precipitating dominant hapten phenomenon through three precipitations and purifications of the anti-dextran precipitins[1] lends support to the concept that single molecules of antibody reacted with both haptens. This immune system should serve as a useful model for further immunochemical study of this and related problems of precipitation, desensitization and specificity of hapten-antibody reactions.

The subject of hapten desensitization needs extensive exploration. In actively sensitized experimental animals, antigens neutralize sensitizing antibodies only transiently *in vivo*. Permanent tolerance produced by treatment with specific allergens occurs only in the states of immunological paralysis[10] and unresponsiveness.[11] Theoretically, suitable haptens should be able to induce permanent desensitization by neutralizing sensitizing antibodies without eliciting more antibodies anamnestically. It is conceivable that the principle of dominant hapten desensitization can be applied to the treatment of allergic phenomena by the use of haptens of pollens, dusts, and other allergens. It is in this setting, with emphasis on desen-

sitization, that these examples of dominant and recessive haptens are presented.

SUMMARY

Two experiments illustrate the phenomena of dominant and recessive precipitating and desensitizing haptens.

1. Type II pneumococcal polysaccharide precipitated all of the anti-Type II and antidextran precipitins from Type II antipneumococcal rabbit serum. Dextran precipitated all of the antidextran but not the anti-Type II precipitins.

2. Type II polysaccharide desensitized passively sensitized guinea pigs against the polysaccharide and dextran, whereas dextran desensitized against dextran but not against the polysaccharide. In both experiments, polysaccharide was the dominant and dextran was the recessive hapten.

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EVALUATION OF A COMBINATION TABLET OF THEOPHYLLINE, EPHEDRINE SULPHATE, PHENOBARBITAL, THENYLDIAMINE AND GLYCERYL GUAIACOLATE IN THE TREATMENT OF CHRONIC ASTHMA

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New York, New York

THE PURPOSE of this study was to ascertain the effectiveness of a combination tablet* of Theophylline 100 mgms, Ephedrine Sulphate 24 mgms, Phenobarbital 8 mgms, Thenyldiamine (an antihistaminic) 10 mgms and Glyceryl Guaiacolate (a mucolytic and expectorant) 100 mgms, in the treatment of bronchial asthma.

The combination of ephedrine and ephedrine-like compounds with theophylline and phenobarbital has had wide clinical acceptance. Such preparations have been found to be effective in the relief of chronic asthma. Rudolph[1] found the preparation consisting of benzylephedrine 30 mg, luminal 8 mg and theophylline 120 mg effective in 85 per cent of the sixty asthmatic patients treated with it over a period of from three to six months. Clein,[2] using the same preparation, has given it to children in one-half tablet doses with satisfactory results. Brown[3] treated a group of 140 patients suffering from bronchial asthma with a capsule containing one-half grain of ephedrine sulphate, one-half grain of sodium phenobarbital and three grains of theophylline sodium acetate. The patients treated with this combination of drugs, when helped, all agreed that the relief came more quickly and was more complete than that given by the usual doses of ephedrine and phenobarbital alone. Brown also used this combination of drugs in an enteric coated tablet which he administered at bed time; he found this tablet extremely effective in the prevention of night attacks of asthma.

Bickerman[4] and his colleagues found the preparation consisting of ephedrine hydrochloride, aminophylline, aluminum hydroxide, ethylaminobenzoate, and sodium pentobarbital effective in 72 per cent of 155 patients. Sheldon[5] found the combination of ephedrine, aminophylline and a barbiturate to be satisfactory in the treatment of mild asthma in geriatric patients. Scherr[6] evaluated a combination tablet of 20 mgs of racephedrine, 27.5 mgs of sodium pentobarbital and 200 mgs of choline theophyllinate in a series of over 100 patients. He found this tablet ideal for the chronic asthmatic with an acute exacerbation of a mild or moderate degree. He noted rapid symptomatic relief in 81.5 per cent of the patients treated.

In order to improve the effectiveness of this widely used combination of drugs in the treatment of bronchial asthma, an expectorant and an antihistamine were added. The need for the addition of an expectorant

*Kindly supplied by George A. Breon and Company as Bronkotabs.

to such a combination of drugs is great because patients with asthma frequently retain bronchial secretions. These secretions narrow the bronchial tubes and add further to the maintenance of partial bronchial obstruction already initiated by bronchospasm; they also cause an increase in tracheo-bronchial spasm and provoke paroxysms of coughing. The antihistamine was added to such a combination of drugs only for its usefulness in the management of patients with both asthma and hay-fever.

Expectorants[7] have been found useful in removing retained mucus or exudate from the tracheo-bronchial tree. Glyceryl Guaiacolate,[7] the expectorant used in the combination tablet under study, has the property of increasing the output and decreasing the viscosity of the respiratory tract fluid and by doing so makes the retained secretions less tenacious and more easily expectorated.

Connell[8] and his colleagues undertook animal experiments designed to evaluate objectively the clinical impression that glyceryl guaiacolate is a drug capable of increasing the liquid secretions in the respiratory tract. They had previously observed, that a dose of 100 mgs of glyceryl guaiacolate dissolved in sweetened water and administered four times daily, orally, to twenty patients, acted effectively by making expectoration easier and freer. The glyceryl guaiacolate given to these patients caused no unpleasant side effects corroborating previous reports that this drug was almost non-irritating to the stomach. In their experiments, Connell and his colleagues studied the expectorant action of glyceryl guaiacolate in 141 albino rats. They measured the water content of the respiratory tract in the experimental animals before and after the administration of this drug intraperitoneally in doses ranging from 0.066 to 6.6 mgs per kilo. They found that the injection of the drug intraperitoneally produced an immediate increase in lung water during the first hour and that this increase was sustained for three days. In seventy-two control rats similarly injected with only equal amounts of saline, no such increase was noted. They concluded that glyceryl guaiacolate acts both as an excretotropic and as a secretotropic agent actually increasing the production and excretion of pulmonary secretions.

Perry and Boyd[9] confirmed the Connell et al findings of the expectorant action of glyceryl guaiacolate by doing the following experiment. They studied the rate of production of respiratory tract fluid in rabbits prior to any drug administration and then measured the rate after the administration of this drug. They collected the fluid from a canula placed in the trachea of a urethanized animal held head downward and inhaling air warmed to body temperature and saturated with water vapor. The hourly output of respiratory tract fluid was first measured for a period of two hours and then following the administration of the drug, for a further period of four hours. The glyceryl guaiacolate was injected intraperitoneally into eleven rabbits in a dose of 0.01 gm per kilo. As a result of the administration of this drug, the respiratory tract fluid in-

TABLE I. CLASSIFICATION OF PATIENTS

Pt.	Sex	Age	Degree of Asthma	Dosage of New Combination Tab.	Concomitant Specific Allergen Injections	Results	Side Effects
1	M	15	Moderate	1 q.i.d.		Good	None
2	M	39	Severe	1 q.i.d.		Fair	None
3	M	8	Moderate	½ q.i.d.		Good	None
4	M	8	Moderate	½ q.i.d.		Good	None
5	F	43	Severe	1 q.i.d.		Poor	None
6	M	10	Moderate	½ q.i.d.		Good	None
7	M	55	Moderate	1 q.i.d.		Fair	None
8	M	68	Moderate	1 q.i.d.		Good	Urinary Retention
9	F	55	Severe	1 q.i.d.		Poor	Jittery
10	F	50	Moderate	1 q.i.d.	Stock dust and bacterial antigen complex	Fair	None
12	M	12	Moderate	1 q.i.d.		Good	None
13	F	6	Moderate	½ q.i.d.		Good	None
14	F	68	Moderate	1 q.i.d.		Fair	None
15	M	59	Severe	1 q.i.d.		Poor	None
21	F	52	Moderate	1 q.i.d.		Good	None
23	M	29	Moderate	1 q.i.d.		Good	None
24	M	75	Severe	1 q.i.d.		Good	None
26	M	29	Moderate	1 q.i.d.		Good	Jittery
29	M	51	Moderate	1 q.i.d.		Good	None
34	M	9	Moderate	½ q.i.d.		Good	None
36	F	33	Mild	1 q.i.d.		Good	None
40	F	54	Moderate	1 q.i.d.		Good	None
16	M	11	Severe	1 q.i.d.		Good	None
17	M	47	Severe	2 q.i.d.	Pollens, stock dust and bacterial antigen complex	Fair	None
18	F	43	Moderate	1 q.i.d.		Good	None
20	F	12	Moderate	1 q.i.d.		Good	None
22	F	51	Severe	1 q.i.d.		Fair	None
25	M	9	Moderate	½ q.i.d.		Good	None
35	M	27	Mild	1 q.i.d.		Good	None
37	F	41	Mild	1 q.i.d.		Good	None
11	M	36	Moderate	1 q.i.d.		Fair	None
27	F	39	Severe	1 q.i.d.	Inhalants, stock dust and bacterial antigen complex	Fair	None
32	F	53	Moderate	1 q.i.d.		Good	None
33	F	51	Severe	1 q.i.d.		Poor	None
38	M	55	Moderate	1 q.i.d.		Good	None
28	M	44	Moderate	1 q.i.d.	Pollens, stock dust and Inhalants	Poor	None
30	M	65	Moderate	1 q.i.d.		Fair	
31	F	43	Severe	1 q.i.d.	Pollens, stock dust, inhalants and bacterial antigens complex	Poor	None
19	F	55	Severe	1 q.i.d.	Bacterial antigen complex	Poor	None
39	F	47	Mild	1 q.i.d.	— — — — — —	Good	None

creased markedly from a twenty-four-hour output of 2 ml/kilo to a twenty-four-hour output of 3½ ml/kilo.

A number of publications have appeared indicating the clinical effectiveness of glyceryl guaiacolate as an expectorant. Cass and Frederick[10] studied the clinical effectiveness of several frequently used cough medications and compared their effectiveness with a liquid preparation containing 100 mgs of glyceryl guaiacolate and one mg of desoxyephedrine. They concluded that the latter preparation was more effective in the treatment of cough for retained secretions than terpin hydrate or ammonium chloride. Schwartz[11] and his colleagues studying this same preparation concluded that it was more effective than potassium iodide in the management of bronchial asthma. They found that this preparation was more helpful in liquefying the mucous secretions and facilitating their expulsion.

CLASSIFICATION OF PATIENTS AND METHOD OF TREATMENT

Table I

Patients selected for treatment all had chronic asthma. This selected group included ten children and thirty adults; the oldest patient was seventy-five and the youngest six years of age. Twelve of the forty patients had severe asthma, twenty-four moderately severe and four mild asthma. The group included twenty-two males and eighteen females.

Thirty-nine of the forty patients were sensitive to stock dust; thirty-seven had a definite history of bacterial allergy or lack of bacterial resistance as manifested by recurrent upper respiratory infections; eleven patients were pollen sensitive and seven were inhalant sensitive.

Children ten years of age or younger were given one-half of a tablet of the medication, four times a day. Children over ten and adults were given a whole tablet, four times a day. Only one patient was placed on two tablets, four times a day. Patients remained on the medication for periods of one to four weeks.

Along with the administration of the medication, specific allergic therapy was carried out in thirty-nine of the forty patients. Hyposensitization inoculations of stock dust extract, pollens, inhalants and specially prepared bacterial antigens were administered concomitantly. Thirty-seven of the forty patients received inoculations of acellular bacterial antigen complex (B. A. C.)[12] prepared by the Hoffmann process.

TABLE II. RESULTS OF TREATMENT

Results	Number of Patients	Per Cent
Good	24	60.0
Fair	9	22.5
Poor	7	17.5

TABLE III. COMPARATIVE RESULTS OF ALTERNATIVE TREATMENT

Total Number of Patients: 20	When Treated With New Combination Tablet	When Treated With Tablet Without Expectorant or Antihistamine
Increase in expectoration	16	4
Greater improvement in asthma	16	4

RESULTS

Tables II and III

Twenty-four or sixty per cent of the forty patients treated obtained good relief of their asthma; nine or twenty-two and one-half per cent obtained fair relief of their asthma and seven or seventeen and one-half per cent failed to respond.

Twenty patients of the group of twenty-four obtaining good relief with this new combination tablet were placed, for alternate periods of

one week, on the conventional tablet containing ephedrine, theophylline and phenobarbital only. Sixteen of these twenty patients reported that the new combination tablet was definitely more effective.

Relief of asthma was accompanied by an increase and ease of expectoration of the bronchial secretions, by reduction in bronchospasm and by an increase in vital capacity. The combination of drugs used in this study gave greater relief in these patients than the conventionally used tablet which did not contain an antihistamine and an expectorant.

TABLE IV. SIDE EFFECTS

Type of Side Effect	Number	Per Cent
Urinary retention	1	2½
Nervousness	2	5
Totals	3	7½

SIDE EFFECTS

Table IV

Side effects were infrequent; only three of the forty patients treated complained of side effects. One patient developed urinary retention and had to stop the medication. Two patients developed mild nervousness which did not cause them to discontinue the medication.

SUMMARY

The combination of ephedrine and ephedrine-like compounds with theophylline and phenobarbital has had wide clinical acceptance. This study confirms previous reports of the clinical effectiveness of glyceryl guaiacolate as an expectorant. It also indicates an additional benefit is obtained by its addition to the conventionally used tablet for relief of mild or moderately severe chronic asthma. The addition of an antihistamine was made to this new combination tablet for the benefit of those patients who have seasonal or non-seasonal allergic rhinitis in association with their asthma. This tablet gave relief with a minimum of side effects. Its use should be in association with the usual specific allergic treatment of these patients.

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PSYCHOLOGICAL AND PHYSIOLOGICAL VIEWPOINTS

We cannot judge our mental processes directly from the physiological viewpoint any more than we can examine a physical process from the psychological viewpoint. This state of affairs makes the body-mind problem appear in a different light. For the examination of psychosomatic processes will yield entirely different results, according as the psychological or the physiological viewpoint is taken as the basis of observation. The psychological viewpoint will permit us to gain first-hand information about physical processes only. It is therefore impossible to gain first-hand information about both physical and mental processes from any single viewpoint; and since in order to reach a clear conclusion we must adhere to a given viewpoint, which automatically excludes the other, the search for the interrelation of physical and mental processes loses its meaning. In this case, there exist only physical processes or mental processes, but never processes which are physical *and* mental.

Therefore, it will do no harm to say that the physical and the mental are in no way different from each other. They are the selfsame processes, only viewed from two diametrically opposite directions. This statement is the answer to the riddle, which has been inseparable from the theory of parallelism, namely, how one is to conceive the fact that two types of processes so different from each other as the physical and the mental, are so closely interlinked. The link has now been disclosed. At the same time, the body-mind problem has been recognized as another phantom problem.—MAX PLANCK (1858-1947) *Scientific Autobiography,* 1949.

PROPHYLACTIC INOCULATION AGAINST HAY FEVER

Historical Document

By L. NOON, B. C. Cantab., F.R.C.S. Eng.

HAY FEVER is a form of recurrent catarrh affecting certain individuals during the months of May, June, and July. It is caused by a soluble toxin found in the pollen of grasses. The patients present the idiosyncrasy of being sensitive to this toxin, which is innocuous to normal individuals. The idiosyncrasy may be detected during any season of the year by dropping a little of an extract of grass pollen into the eye of the suspected individual; a reaction, described more fully below, will be obtained in the case of a hay fever patient, but a normal man will show no effect.

Bostock (1819)[1] recognized the seasonal recurrence of hay fever as separating it from other forms of catarrh. Blackley (1873)[2] advanced much evidence in favor of the pollen theory of its causation, but we owe chiefly to Dunbar (1903)[3] the exhaustive scientific proof of this theory. Dunbar showed that not only all the mucous membranes but even the skin of hay fever patients is sensitive to pollen toxin in a way not shown by normal individuals. He also proved that the injection of the pollen toxin gives rise in animals to the production of an antitoxin having a specific power of neutralizing this toxin. Further, in hay fever patients, he showed the occurrence of some of the reactions associated with the production of immunity:—namely, a specific precipitation of pollen extracts by the patient's serum, and the phenomenon of complement deviation, during the hay fever season, and persisting for a short time after this. Pollen toxin is, therefore, a body capable of giving rise to the production of antibodies in animals and in hay fever patients, subjected to its action. It is also undoubted that hay fever patients sometimes become cured of their idiosyncrasy. The most reasonable explanation of this phenomenon would seem to be, that the cured patients have had the good fortune to develop an active immunity against the toxin, to the action of which they have been liable for so long.

The repeated absorption of toxin at short intervals is, however, more likely to induce a condition of hypersensibility, and this is the more usual fate of the patient who becomes only more sensitive during each succeeding season. The local application of a specific serum, such as pollantin, offers a reasonable method of treatment, but one which is difficult and

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From the Laboratory of the Department for Therapeutic Inoculation, St. Mary's Hospital.

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laborious, and which is not calculated to bring about a permanent cure. Cures are, indeed, ascribed to the use of this remedy but admittedly in exceptional cases; and where the conditions are not understood and the experience is not constantly repeated, one must hesitate to attribute the result to the cause cited. On general grounds a much more satisfactory result would be expected from the induction of an active immunity, and it seemed worthwhile to put this expectation to the test of experiment. The questions, to be answered are as to what degree of immunity can be induced in hay fever patients by inoculations of pollen toxin, how these inoculations may best be regulated, and whether the affection can by this means be permanently cured.

With this end in view, the experiments here described were undertaken in the past autumn, winter and spring to study the reactions of hay fever patients towards innoculations of pollen toxin. The off season of the year, when the patients were not exposed to spontaneous innoculations, was favorable to this investigation, as the scheme of dosage was then not liable to be upset by spontaneous absorption of toxin from the air, laden with actively poisonous pollen grains. The plan of experiment was to obtain a numerical measure of the sensitiveness of the patients to the pollen toxin and to observe whether this was increased or decreased by subcutaneous inoculations of various quantities of pollen toxin. These observations can be conveniently carried out by the method described below, and it was found that, with well-regulated dosage, it was possible in every case to raise the patients' resistance, to a marked degree, within the lapse of a few months, while, on the other hand, ill-regulated dosage was at once made evident by a decrease in the resisting power.

The pollen extract used was prepared by Dunbar's method of extraction with distilled water, aided by freezing and thawing several times. The extracts were boiled for ten minutes after having been sealed in glass tubes; this treatment was not found to decrease their activity at all. The pollens tested were grass pollens of different species—*Phleum pratense, Poa trivialis, Holcus lanatus,* and *Agropyrum caninum.* These pollens were all found capable of exciting an energetic reaction when instilled into the conjunctival sac of hay fever patients. Timothy grass *(Phelum pratense)* was found to yield the most active extract, and this extract was consequently used throughout the rest of the experiments. One gramme of pollen was extracted with 50 cc of water. The activity of this extract may be judged from the fact that one drop of a five-thousand-fold dilution is sufficient to excite a distinct reaction in the conjunctiva of the more sensitive patients.

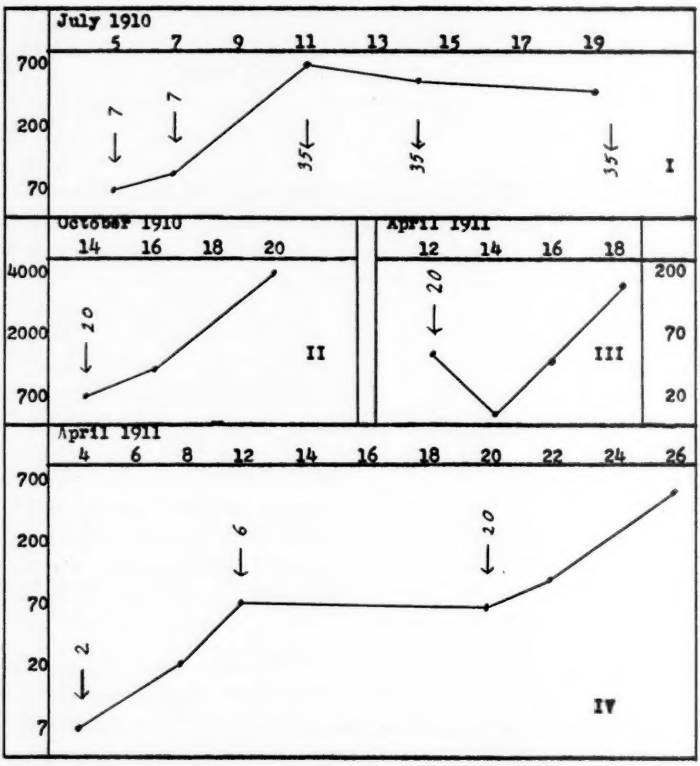
In order to express the strengths of pollen extracts used in testing patients and the doses of pollen toxin given subcutaneously, a unit of pollen toxin has been arbitrarily chosen. This unit is the quantity of pollen toxin which can be extracted from the thousandth part of a milli-

gramme of *Phleum pollen*, and it has the advantage that all the quantities used can be expressed in whole numbers. The strength of a pollen extract is given below in terms of the number of such units contained in a cubic centimetre of the extract. Extracts of other pollens have been standardized against the Phleum extract by comparative tests on the eyes of hay fever patients.

A measure of the patient's resistance during the experiments is obtained by observing the strength of pollen extract necessary to excite a conjunctival reaction. One drop of the diluted extract is instilled into the eye. The reaction obtained consists in a reddening of the caruncula and, to a lesser degree, of the palpebral conjunctiva, together with a slight injection of the vessels of the ocular conjunctiva and some lacrymation. The patient experiences a feeling of burning and itching. These signs reach a maximum in about five minutes, and a little later there may be a slight attack of sneezing. The reaction lasts as a rule about half an hour. The strength of the extract, which is just sufficient to give this reaction, is used to describe the resistance of the patient. The most sensitive patients examined gave before treatment a distinct reaction with a dilution containing only 4 units per cc, their resistance is described as four; the least sensitive reacted to a strength of 70 units per cc, or, in other words, had a resistance of seventy. Normal individuals fail to react with the strongest extract (Strength 20,000 units) and even resist the application of fresh pollen dust to the conjunctiva. Their resistance is, therefore, by our scale, more than 20,000 but it is not infinite as a cubic centimetre of this extract injected beneath the skin of a normal man has been found to give rise to a slight local swelling and tenderness, lasting for about twenty-four hours.

Course of immunization.—Patients received subcutaneous injections of pollen extract. At first very minute doses were given at intervals of three or four days (Fig. 1), and the resistance of the patients rose rapidly; on increasing the dose however, it was found that the resistance ceased to rise and even went back towards its original value. Longer intervals were then allowed to elapse between successive inoculations. The patient to whom Fig. 1 refers had a three months respite and after that interval, responded to a moderate dose in the way shown in Fig. 2. It is not necessary, however, to leave such a long interval as this between the doses: ten days or a fortnight are, as a rule, sufficient, and at the beginning of treatment, when small doses are being given, a week is enough (Fig. 4). After some time, when the resistance has been considerably raised, small doses cease to have any effect. On increasing the dose it is found that the first effect of the inoculation is to lower the resistance for a few days, giving a negative phase, after which the resistance rises again and passes beyond its former maximum (Fig. 3). Ultimately a stage is reached at which the resistance, as measured by

the ocular test, ceases to rise, or rises so slowly that the alteration is only obvious after prolonged observation. At this stage the patients will withstand gradually increasing subcutaneous inoculations without showing a negative phase. In the early stages of immunization it is possible,



The numbers at the sides denote the resistance of the patient, given in terms of the strength of pollen extract, one drop of which was sufficient to excite a conjuctival reaction. The arrows indicate subcutaneous inoculations of pollen extract, quantities given in the units described in the text. Figs. 1 and 2 refer to one patient at different periods of treatment; Fig. 3 shows the response obtained after about a month's treatment in another case; and Fig. 4 the early stages of treatment.

by an overdose, to induce a severe attack of hay fever lasting nearly twenty-four hours; this has not been observed in the later stages.

The result of these experiments so far is to show that the sensibility of hay fever patients may be decreased, by properly directed dosage, at least a hundredfold, while excessive or too frequent inoculations only serve to increase the sensibility. It still remains to be seen whether the

immunity thus attained is sufficient to carry the patients through a season without suffering from their annual attacks of hay fever. Patients are under observation who have undergone treatment for periods varying from a few weeks to eight months.

It is hoped that these cases will afford material for a further report after the present hay fever season. This work is now in the hands of my colleague, Dr. J. Freeman, who very kindly came to my assistance and carried on the observations during my enforced absence of some months.

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DARWIN'S INTRODUCTION

This abstract, which I now publish, must necessarily be imperfect. I cannot here give references and authorities for my several statements; and I must trust to the reader reposing some confidence in my accuracy. No doubt errors may have crept in, though I hope I have always been cautious in trusting to good authorities alone. I can here give only the general conclusions at which I have arrived, with a few facts in illustration, but which, I hope, in most cases will suffice. No one can feel more sensible than I do of the necessity of hereafter publishing in detail all the facts, with references, on which my conclusions have been grounded; and I hope in a future work to do this. For I am well aware that scarcely a single point is discussed in this volume on which facts cannot be adduced, often apparently leading to conclusions directly opposite to those at which I have arrived. A fair result can be obtained only by fully stating and balancing the facts and arguments on both sides of each question; and this is here impossible.—CHARLES DARWIN (1809-1882) Introduction to *Origin of Species.* (From *The Development of Modern Science,* Edited by George Schwartz and Philip Bishop, New York: Basic Books, 1958.)

Progress in Allergy

DERMATOLOGIC ALLERGY VI

Critique and Review of the Recent Literature

JOHN L. FROMER, M.D., F.A.C.A.
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THIS IS THE sixth annual review of the current literature as it relates to dermatologic allergy. The most interesting and instructive articles have been abstracted from a number of sources. A number of reprints of original articles in this field are regularly received by the reviewer, for which he is grateful. The *Review of Allergy and Applied Immunology* and the *Yearbook of Dermatology and Syphilology* serve as superb criteria for material in this field.*

Biochemistry and genetics offered outstanding advances in medicine in the past year. The Nobel prize was given to Tatum, Beadle and Lederberg in recognition of their advanced work in these fields. Biochemical studies[56] of genes and of viruses indicated a similar structure with nucleic acid at the center, surrounded by proteins of varied structure and form. It is hoped that advances of this type can be extended to explain some of the mysteries surrounding basic patterns in immunology and allergy. Studies of the auto-immune diseases; fluorescent antibody in disseminated lupus erythematosus; other precipitating reactions in this disease and rheumatoid arthritis may lead to a greater understanding of the problem by the allergist. While the latter continues to make important clinical observations the real solutions will undoubtedly come from the laboratory team of biochemists, immunochemists and physicists, enzyme chemists and others interested in basic sciences.

This review is divided for convenience into the following subsections: (1) allergic eczematous contact dermatitis, (2) atopic dermatitis, (3) urticaria and angioneurotic edema, (4) drug allergy, (5) steroid hormones, and (6) miscellaneous allergies.

ALLERGIC ECZEMATOUS CONTACT DERMATITIS

Experimental Studies.—Multiple eczematous sensitivities which are regularly seen and therefore of greatest practical importance in clinical dermatology are discussed by Baer.[5] These have been divided for convenience into three categories. The first is multiple non-specific eczematous

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*An abridgment of this review will be published in *Review of Allergy and Applied Immunology.*

sensitivity, the mechanism for which is a low threshold to the effects of primary irritants. This is not an immunological phenomenon, and non-specific factors are highly important. There are usually no immunochemical relationships of antigens or materials, and the duration of multiple sensitivities may be evanescent—weeks to months. It is known that reactivity to primary irritants varies greatly in different persons even under normal conditions. Even in safe dilutions, mercuric chloride, 1 to 1000, may produce a small percentage of reactions as a primary irritant. In this state, if patch tests are carried out, non-specific positive reactions may be elicited with normally non-irritating concentrations of many diverse materials. This increased irritability may persist for three or four months after an eruption has subsided. Other contributors to this state are impaired alkali neutralization, disturbances in sweating, bacterial, viral and mycotic infections, a seborrheic and/or psoriatic tendency, and photosensitization. The production of acanthosis (as with some detergents) engenders a state of multiple non-specific irritability.

The second category includes multiple allergic eczematous sensitivities of the primary type. These are shown in individuals who have an abnormal capacity to undergo primary allergic sensitizations. Patients in whom multiple primary allergic sensitizations develop are more prone to the development of other cutaneous sensitizations than are patients with nummular eczema and atopic dermatitis. The susceptibility to true eczematous sensitization of patients with atopic dermatitis is no greater than in normal control subjects. The cause for this type of sensitization is not understood. It is presumed that a genetic factor may be involved, but no conclusive evidence for this exists.

The third category is that of multiple allergic eczematous sensitivities of a secondary nature. This is the group in whom cross-sensitization reactions develop from allergens which are closely related immunochemically. Examples of this are the multiple sensitizations to various Rhus allergens which have a catechol as the underlying component of the allergen, or a primary allergen which may be converted, either reduced or oxidized, in the body into compounds that are immunochemically related to the secondary allergens. Picric acid sensitization may predispose individuals to reactions with local anesthetics and dyes. Further examples of conversion, primary and secondary allergens, are present among halogenated hydroxyquinolines and substances such as iodochlorhydroxyquin (Vioform), diiodohydroxyquin (Diodoquin) and chlorquinaldol (Sterosan), all of which are broken down to carboxylated pyridines that produce cross-sensitization. Ingestion of azo dyes in foods may initiate flare-ups in patients with allergic hypersensitivity to paraphenylenediamine in hair and fur dyes. Cross-sensitization exists between streptomycin and neomycin. Repeated exposure to the primary allergen does not produce additional cross-sensitization. It is known, however, that the more intense the degree

of primary sensitivity, the more likely it is that multiple secondary sensitizations will occur.

Gaul[66] studied a number of patients who were primarily nickel sensitive, since multiple reactors are common when doing diagnostic patch tests. Histories were carefully taken and patch tests were made with various preparations which the patient had previously applied. There was an inorganic battery of tests containing common metals, such as potassium chromate, nickel sulfate, gold chloride, mercuric chloride, and so forth. The organic tray consisted of merthiolate, formalin, monobenzylether of hydroquinone, paraphenylenediamine, benzocaine, resorcin and an epoxy resin, as well as a few other agents. Screening patch tests carried out in 1957 on 234 office patients showed nickel sensitivity in eighteen; two of the tests were classified as false-positives. The inorganic sensitivity group consisted of seven patients and they were sensitive, for the most part, to nickel. This was associated with minimal dermatitis, low attack rates, and few, if any, symptoms. In the combined sensitivity, however, inorganic and organic, multiple sensitivities were associated with acute dermatoses, often extensive in distribution, with a high attack rate and severe symptoms requiring long periods of cutaneous disability. In the nine cases with inorganic as well as organic sensitivity, such agents as the caines, mercury, chromates, hair dye, paraphenylenediamine and perfume entered into the picture of broadening of the base of contact sensitivity.

Frey and Wenk[60] studied the influence of Calmette-Guérin bacillus infection on dinitrochlorbenzene contact eczema of the guinea pig. It was found that sensitization of the guinea pig's skin with this agent was potentiated if there was an intracutaneous inoculation with Calmette-Guérin bacillus at the same time, and in the same skin area. It was presumed that the antigens reached the same group of regional lymph nodes. If the antigens were applied to separate skin areas, to reach a different set of lymph nodes, potentiation was minimal or even absent. It is to be remembered that the authors have also shown that sensitization does not subside with the simple removal of regional lymph nodes once sensitization has been established, so it is believed the lymph nodes are not the only source of antibody production, but that other organs can progressively produce antibodies.

Bridges and others[29] presented detailed investigations of an immunologically normal child born to a woman with acquired agammaglobulinemia. Careful studies revealed gammaglobulin concentrations in the baby to be below 11 mg per 100 ml until the sixth week of life. Antibody did not appear in the serum in spite of intensive antigenic stimulation until the sixty-seventh day of life. Serial bone marrow and lymph node biopsies did not reveal plasma cell production at any time during the neonatal period. Plasma cells appeared concurrently with the capacity to synthesize gammaglobulin and antibody. In the rabbit, plasmacytosis in response to even intense antigenic stimulation does not occur before the age of sixteen days.

Baer and others[9] studied the effect of feeding simple chemical allergens (picryl chloride or dinitrochlorbenzene) to pregnant guinea pigs. Later, when the offspring of these animals were full grown, they were sensitized to the same agents by topical application and intramuscular injection. The offspring of the treated animals, when compared with controls, showed a slight but consistent diminution of capacity to become sensitized to the specific allergen. It was thought that this pilot study would warrant further investigation.

A number of experiments with mercaptans of low molecular weight were made by Voss.[215] These agents are related to the thioglycolates which have a widespread use in hair waving. It was shown that forty of forty-four compounds were found capable of sensitizing man and/or the guinea pig. In this work the guinea pig was less readily sensitized than man. The use of Freund's adjuvant combined with mercaptan greatly increased the sensitizing potential of the test compound. It was even possible to sensitize guinea pigs to thioglycolate, using Freund's adjuvant. It is to be noted, however, that thioglycolate, which has been used widely in cosmetic products by millions of women, has little or no sensitizing potential.

Seasonal ragweed dermatitis is well known and has been described frequently in the literature (J. L. Fromer and W. S. Burrage, 1953). The common type is the sensitivity to the ether-acetone-soluble pollen fraction, "ragweed oil." However, there is a type of ragweed dermatitis caused by inhalation of the pollen in which the challenging exposure occurs through the inhalant route. Cohen[39] found two patients who showed the coexistence of atopic and contact factors in ragweed hypersensitivity. Because of the possibility that both contact and atopic sensitization might have been mediated by related ragweed antigens, techniques involving experimental sensitization were attempted. Circulating precipitating antibody against one major antigenic component of the water-soluble fraction of ragweed pollen was detected in the sera of rabbits immunized with the ether-soluble fraction of the pollen grain ("pollen oil"). The oil constituent demonstrated evidence of immunologic identity with one of the antigenic components of the aqueous pollen fraction. Possible explanations for these experimental findings and its relation to the dual immunologic mechanisms of immediate and delayed types of cutaneous hypersensitivity are discussed.

Twenty-four patients suffering with eczema were studied by McCallum[118] with special reference to the histopathology of contact eczema and its association to sweat retention. Forty-five biopsy specimens were obtained. From these studies it seemed that the sweat ducts high up in the dermis were resistant to rupture when involved in the eczema reaction. They could be elongated and compressed between vesicles which were closely situated. However, frequent rupture at the lower level of the stratum corneum was noted in the sweat duct. This could explain sweat retention syndromes previously described by Sulzberger and Herrmann some years ago. In acute contact dermatitis, changes were noted in the epidermal cells

of the hair follicles, and in some cases vesicles occurred in association with the hair follicle. It is possible that this is evidence for the entry of allergens through the dermal appendages. As is well known, the changes in the epidermis were found to be essentially destructive and those in the dermis were exudative in character. The reviewer notes that great strides have been made in the past few years with special reference to the mechanism of the formation of the vesicle and bullae in the skin. Studies of this nature are exceedingly helpful.

A study was undertaken by Becker and O'Brien[11] in patients who have a primary dermatitis with a more or less generalized secondary dermatitis as a result of auto-eczematization. It has been thought that this disorder constitutes allergic reactions to products of secondary infecting organisms, either alone or in combination with substances derived from epidermal cells and keratin. Furthermore, it has been shown that bacterial products, when used as patch tests, produce eczematous reactions. Most of these patients had positive bacterial cultures, almost exclusively coagulase-positive hemolytic *Staphylococcus* (*micrococcus*) *pyogenes var. aureus.* In order to rule out local eczematous factors, a number of patch tests were made in 110 patients. Reactions to nickel, chrome, copper and fluoride were usually follicular or poral in nature. Serial biopsy in patients with folliculoporal reactions showed that the primary reaction is dermal, with secondary folliculoporal epidermal vesiculation, which was interpreted as fundamentally dermal in origin. Hence, in the patch test interpretations, the eczematous reactions signified that the patient's primary dermatitis may have been the result of epidermal allergic reaction, while positive folliculoporal tests suggested dermal allergy and that the primary dermatitis is more likely to have been functional in nature. If all the tests were negative, primary functional dermatitis was suggested. Folliculoporal reactions were found most frequently in patients with functional dermatitis.

Clinical Aspects.—The Committee on Occupational Dermatoses[19] presented a survey on occupational dermatoses—the most frequently encountered industrial disease. Predisposing factors are discussed. The type of skin, presence and absence of small or large amounts of pigment and the amount of sweating are factors which contribute to a dermatitis of the sensitization type or from primary irritants. Metabolic disorders may decidedly affect the tolerance of the skin to maintain its integrity. Patients with diabetes are susceptible to fungus and bacterial infections of the skin. The normal skin is impermeable to water and electrolytes, owing to the impermeability of the stratum granulosum and stratum lucidum. Damage to the skin breaks this barrier. Pre-existing dermatoses, such as atopic dermatitis, lichen planus, psoriasis or stasis dermatitis, may predispose a patient to subsequent skin involvement. The ten causes in a classification of occupational dermatoses are as follows: petroleum products and greases; alkalies and cement; solvents; plants and woods; metals and metal plating;

rubber and its compounds; burns, physical and mechanical agents; chemicals, unspecified; paints, enamels and varnishes; acids and acid fumes; dyes and dye intermediates. In 80 per cent of industrial dermatoses, the offending agent is a primary irritant and is usually an acid, alkali or solvent. Cure and improvement of a contact dermatitis can be achieved by eliminating the contacting substance.[20] Proper local therapy, the use of protective clothing, job change and complete discontinuance of work for varying periods are also important measures. The problem of prolonged and recurrent industrial dermatitis raises the question of incorrect dermatologic diagnosis, failure to establish the cause, and failure to eliminate the cause after its discovery and diagnosis. Often improper medication and development of secondary infection, nummular eczema or dyshidrosis may prolong a contact dermatitis. Finally, one must consider poor facilities, improper cleansing agents and cross-sensitivity, which have been overlooked. Cross-sensitivity can occur to procaine, pontocaine, butesin, ethyl aminobenzoate, sulfonamide, *p*-aminobenzoic acid, aminosalicylic acid, azo dyes and paraphenylenediamine. These agents have a similar amino group in the para position of the benzene ring. If a patient is prone to recurrent contact dermatitis, he should not be placed in hazardous new work that requires contact with primary irritants or sensitizers. In an analysis of factors which prevented the recovery of an industrial dermatitis, Morris[126] enumerated twenty-four causes in an article published in 1954. Five additional causes for prolonged and recurring dermatoses are listed in five case reports which are presented. These include: (1) taking a hot bath, (2) strong liniment applied for backache, (3) radiant heat, (4) varicose veins, and (5) naphtha fumes in a patient sensitive to this agent.

In a recent article[18] on occupational dermatoses, the Council on Industrial Health emphasizes that of the cases of contact dermatitis, approximately 80 per cent are caused by primary irritants, which include organic and inorganic acids and alkalies, corrosive salts, reducing agents, petroleum oils, solvents, tar and pitch. In approximately 20 per cent of the cases, occupational dermatoses are caused by sensitizing agents. These sensitizers include dye intermediates, dyes, natural and synthetic resins and waxes, bichromates, rubber compounds, accelerators, photosensitizers and explosives. In searching for the cause of an occupational dermatitis, it is important to check on skin cleansers used at work as well as on the extracurricular activities of the patient, such as hobbies and work around the home. Successful handling of industrial dermatoses requires a knowledge of plant operations and a reasonable degree of skill in dermatological diagnosis.

In discussing medico-legal aspects of occupational dermatoses, the Council on Industrial Health[21] noted that thousands of occupational dermatoses claims are compensated each year. The first workmen's compensation law in the United States was passed in 1908 by the federal govern-

ment, and this applied chiefly to civil employes. In 1911, the states formulated compensation laws. These laws vary considerably among the states in scope, coverage and benefits. There is a lack of uniformity in the interpretation and application of such laws. This results in many problems in litigation of an injury and illness, including dermatitis incurred from work. An occupational dermatitis has been defined as an inflammatory condition of the skin incidental to one's occupation. This might, however, include housewife's dermatitis, plant dermatitis in the florist, and a dermatitis in the architect as caused by his teakwood ruler. As is well known, there may be great difficulty in determining whether the cause for a given cutaneous eruption is industrial in nature.

A number of cases are recorded which indicate how difficult it may be to judicate a particular type of industrial case. Problems of hypersensitivity, new injury or recurrence, aggravation, disfigurement and patch tests are discussed in considerable detail. The legal aspects of several cases are discussed, with close follow-up of the opinions from court to court. Many of these are diametrically contradictory opinions and may vary from state to state. A disfigurement may be compensable. The case is cited of a patient in whom an extensive keloid formation developed which disfigured her arm; it was found that this constituted a disability, and compensation was awarded. Patch tests may be admitted as evidence if the physician performs and interprets the test himself. Commissioners and lawyers have considerable difficulty interpreting false-positive, false-negative and delayed reactions to patch tests. A case is cited in which a patient's condition was made worse by a patch test using a Chinese plant as antigen. A number of questions pertaining to the liability of the patient or physician are involved. In Massachusetts, the opinion was held that the physician could not be liable for any undue reactions from patch tests. The aggravation or extension of the original dermatitis by the patch test was considered compensable by the Board. The insurer is liable for all the consequences which flow "as a rational result" from the original injury.

Various common types of occupational dermatitis are described by Morris.[131] Insoluble cutting oils generally cause blackheads, papules and pustules. Other non-specific effects are seen but rarely sensitization dermatitis. This is caused by the soluble cutting oils which rarely produce the comedo types of dermatoses. Studies with oils "tagged" by fluorescent materials have indicated that ordinary cleansers do not remove the oil adequately. Liquid sulfonated oil cleansers seem to work well, and the reviewer has had good success with a preparation called "Lixoil." The types of dermatitis usually seen and the treatment for each type are described. Protective measures and other aspects of occupational dermatitis are also presented. Hellier[74] made a study of 124 employes who had been examined four to six years previously for industrial dermatitis. Of this number, ninety-five had recurrent attacks of dermatitis and earning capacities had diminished to a high degree in these patients. If an

employee was first troubled with a primary irritant, he had more chance of having recurrences than did employees who had industrial dermatitis from allergenic hypersensitivity. The results of this study at least suggest that permanent clearing of a dermatitis and freedom from subsequent attacks rarely occur except with a complete change of working conditions.

Buckley[32] describes lichenoid-type lesions following contact dermatitis in photographic operators who handle certain *p*-phenylenediamines. These aromatic amines are used in the manufacture of chemical intermediates, dyes for furs, antioxidants for gasoline, antioxidants for rubber, and as color developers in the photographic trade. This type of sensitization leads to two common clinical forms: the first, seen in about 10 per cent of the total cases observed, is an intense eczematous response followed later by a lichenoid appearance; the second group is the subacute type in which the lesions develop slowly and appear lichenoid from the onset. At times the dry papules are indistinguishable clinically from the papules of lichen planus. Healing progresses as in other forms of contact dermatitis, leaving a slowly regressing pigmentary change. In patch testing, the chemical to be applied to the skin is freshly prepared by appropriately diluting it with distilled water to make a 1 per cent solution. The patch is removed within twenty-four hours and the skin is washed gently with an acid-type skin cleaner to prevent the antigen from becoming fixed to the epidermal cells, which might lead to sensitization by the patch test. Canizares[36] presents the case of a twenty-eight-year-old Puerto Rican man who recently noted an eruption on the dorsal aspects of the fingers which later spread to the arms, neck, face and inner aspect of the thighs. Increased pigmentation in diffuse form was seen on the flexor aspect of the forearms and the dorsal aspect of the hands, forearms and face. Pigmentation was diffuse and on the dorsal aspects of the hands and fingers were several raised, well-defined plaques of a purplish color. This case was presented as an example of a lichen planus-like eruption caused by chemicals handled in the processing of color film. In discussion, there was a difference of opinion as to how a lichen planus-like eruption can develop from an allergic eczematous contact dermatitis. The question of inhalation or ingestion of the chemicals or agents related to them was discussed. One of the dyes used in photography is yellow, which possibly is similar chemically to quinacrine (Atabrine). In World War II many lichenoid eruptions were caused by the ingestion of Atabrine.

Silberman and Sorrell[188] describe their experiences with allergy in fur workers, with special reference to paraphenylenediamine. Of eighty fur workers studied over a fourteen year period, asthma occurred as the sole symptom in thirty patients, vasomotor rhinitis appeared in thirty-eight patients, and five patients had three major symptoms—bronchial asthma, vasomotor rhinitis and contact dermatitis. The only effective approach for the respiratory allergy was complete avoidance, although it was noted that in a few patients with dermatitis to paraphenylenediamine, the patients could

be controlled by the use of protective skin creams. While many patients with respiratory allergy to paraphenylenediamine gave a positive patch test, the most reliable evidence of respiratory sensitivity to this agent is a positive inhalation test to the substance.

Birmingham[17] studied the scope of occupational dermatoses caused by cutting oils. According to available figures, in 1950 approximately 529,000 machinists were employed in this country. In 1952 statistics indicated that 19 per cent of 6,700 occupational cases gathered from eleven states were due to petroleum products, including cutting oils. The opinion is expressed that the high incidence of dermatitis from cutting oils is the result of a number of factors, but principally a lack of personal and industrial cleanliness. A workable program, therefore, in the prevention of occupational dermatoses is outlined by Birmingham. This includes education of management, as well as workmen and supervisory personnel. It is important to enlist the support of the industrial physician, industrial hygienist, nurse or safety committee. The men must be taught personal hygiene, which is attained through protective clothing and ample facilities for cleansing with the proper agents. Sulfonated oil liquid soaps or powdered soaps which contain cornmeal are effective in removing cutting oil from the skin. One of the greatest problems is the fact that the country is dotted with tiny machine shops in which standard controls are difficult to establish.

Downing[46] has reviewed a number of the recent contributions to the subject of dermatitis. Cement dermatitis has, over the years, been regarded as resulting from primary irritation caused by the physical properties of cement. Reports have appeared, however, which show that dermatitis in cement workers may be caused by a specifically acquired allergic hypersensitivity to water-soluble chromate compounds present in cement.

A general survey of dermatitis in industry with special reference to oils was made by Braun and Sitgreaves.[28] This survey involved thirty-six companies with 103,586 employes. Various categories of industrial work in geographic areas were studied. Most of the plants involved exposures to such agents as acids and alkalies, cutting oils, solvents and greases. For production workers, the incidence of industrial dermatitis was reported as 1.2 per cent. It is of interest that the rates for women who were production workers were roughly twice that for male production workers. Merlescu[122] made a study of 206 engine drivers and stokers affected by various dermatoses. Oil folliculitis as well as occupational melanoderma, facial telangiectasia, traumatic pigmentation of the right forearm in engine drivers, and palmar keratoderma were noted. Oil folliculitis was especially prevalent among the stokers.

In these reviews, experiences with a new class of compounds called epoxy resins have previously been reported. Lea and others[102] discuss the irritating and sensitizing capacity of epoxy resins. The increasing use of these resins in various industrial processes has resulted in a very high incidence of contact dermatitis. In a discussion with a leading industrial

dermatologist, this reviewer learned that many of these agents were given industrial sanction long before their sensitizing capacities were known. The generic name for these compounds is derived from the fact that they are polyethers with terminal epoxy groups. They have a wide range of viscosities and the desirable properties of these resins are obtained only after they are combined with curing agents and in this way are converted into mechanically strong polymers. The curing agents (hardeners) are polyfunctional amines; these agents likewise range in viscosity from liquid to solid. As a rule, the cured polymers have little sensitizing capacity. Lea and others studied the irritating and sensitizing properties of one uncured resin, one uncured resin modifer, and four amine curing agents by means of patch testing. The uncured resin and resin modifier were found to be irritating and sensitizing, and three of the four curing agents tested were irritating, but less severe, sensitizers than the resins. Several concentrations of each compound were used. It would appear that usage tables will have to be worked out for most of the compounds now available. The epoxy resins which are now widely used in American industry were apparently introduced long before any serious studies of their sensitizing properties were made. Birmingham[16] has made clinical observations on cutaneous effects associated with curing epoxy resins. The problem is not only that of American industry, but has also arisen in Great Britain, the Netherlands, and Switzerland, where considerable epoxy research and development originated. As has previously been described in these reviews, the epoxy resins have a wide use in the manufacture of electric equipment, castings for tool and die materials, surface coatings, aircraft applications and various adhesive properties. Some of the epoxy resins themselves are irritants and sensitizers, but the diamine or triamine curing agents also produce dermatoses by sensitization. Since the entire industry is so new, the various fabrication practices are crude and not yet standardized. This allows for a great deal of contact with these irritants and sensitizers. It is of interest that the cured product may be handled with impunity.

Morris[125] has been interested in the problem of shoe dermatitis since this is a basic New England industry, and also since he sees a number of these patients for study and treatment. It has been found that the chromium, which is used in tanning most hides into shoe leather, cannot cause dermatitis inasmuch as it is not "hexavalent," and secondly that this chromium is firmly fixed in the leather and cannot easily be removed. Morris[125] believes that both of these principles are incorrect, and that chrome can be leached out of shoes by perspiration and deposited on the skin. Since the leather chemist deposits a basic chromium sulfate in the hide fibers and fibrils, this chemical was used in a 0.2 per cent strength. Four patients with leather dermatitis gave positive reactions to this antigen. One patient sensitive to dichromate antirust fluid used in diesel engines was found to have a positive patch test to 0.2 per cent solution

of sodium dichromate but a negative patch test to 0.2 per cent basic chromic sulfate. In this way, specific sensitivities to chrome salts can be identified. The manufacture of leather, chrome tanning, and clinical aspects of shoe leather dermatitis are discussed. This is the first report that makes use of the basic chromic sulfate solution for testing patients suspected of having a shoe dermatitis. In a further discussion of chrome dermatitis, Morris[129] emphasizes that patients so sensitized must avoid all contacts with chrome, especially in shoes and gloves. This is also true for patients sensitive to nickel. Patients suspected of being sensitive to shoe leather should be tested with a basic chromic compound (trivalent) in 0.2 per cent concentration. The differentiation of specific and non-specific positive patch tests in a case of chromate sensitivity was determined by Gaul[64] in a survey of 844 patients over a three-year period. In the presence of acute mercurial sensitivity, a non-specific chromate response may be induced at the time of patch testing. When the mercury dermatitis subsides, the chromate test is usually negative. An urticarial response to chromate is likely to indicate the presence of another and more severe metal sensitizer which should be investigated. A negative patch test to chromate is decisive.

Sweat band dermatitis[128] has a low incidence due to the fact that chrome-tanning compounds are not used in the preparation of sweat bands. Vegetable tannins which are used are not potent sensitizers. Avoidance of chrome-tanning is desirable since lactic acid and lactate portions of human perspiration can leach chrome salts from chrome-tanned leather. Subsequent deposition onto the skin results in sensitization dermatitis. The basic chromic sulfate is not related to either chromates or dichromates. Soluble chromates and dichromates form yellow and orange solutions for the most part, whereas the basic chromic sulfate salt found in chrome-tanned leather forms a green solution. Basic chromic sulfate compound is available for patch testing and has produced positive patch test reactions in a 0.2 per cent solution. Three cases of typical sweat band dermatitis are presented by Morris: one from paper and the other two from rubbing substances onto the sweat band by the hands.

van der Meer[211] describes the case of a technician in whom contact allergy to copper and zinc developed, manifested by attacks of eczema which responded to steroid therapy. In treatment, zinc oxide ointment was used and it was noted that in his work he had contact with zinc and also with copper in the form of wire. The patient showed patch test reactions in fairly high dilution. Copper reacted at 0.01 per cent; zinc produced a reaction at 1.0 per cent. There was no cross-sensitivity in this case to nickel and bichromate on patch test. The reviewer notes that zinc is freely used by dermatologists in lotions and ointments, with minimal sensitization. Gaul[65] investigated the dermatitis from metal spectacles, using old frames and many which had undergone corrosion at the ear pieces. A greenish deposit was usually found on these old, corroded

metal parts. This proved to be a compound of nickel, probably admixed to some extent with a compound of copper. Patch testing proved that these corrosion products were primary irritants, and this may be the reason for ultimate sensitization to nickel in this area. An alloy of copper and nickel proved to be non-reactive, while an alloy of copper, nickel and zinc was reactive.

The question[154] was raised whether a patient could be desensitized to nickel. The consultant stated that sensitivity to nickel could be determined only by patch testing with a 10 per cent aqueous nickel sulfate solution. A rare instance is reported in the literature of patients being desensitized by the subcutaneous injection of nickel sulfate solution. Attempts at desensitization to nickel by patch testing and by ionization have not been successful. Spontaneous hyposensitization to nickel may occur within months to two years if the reaction to patch test is 2+.

A study of immunologic prophylaxis or hyposensitization against Rhus dermatitis was made by Kligman.[96] The measurement of hyposensitization is exceedingly difficult because there are so many variables. The exact degree of exposure is never known. The pure synthetic allergen, 3-n-pentadecylcatechol (PDC), was used for patch testing throughout the study. The greatest dilution that produces a visible reaction is the best criterion of the degree or depth of sensitization. More than 2000 subjects participated in this study. Placebo hyposensitization was demonstrated by sixteen of eighteen patients who were given injections of sesame oil only; seven reported that for the first time in years they had no dermatitis whatsoever, and nine had only trivial eruptions. Patient satisfaction, therefore, is not a reliable measure of efficacy. Intramuscular prophylaxis with pentadecylcatechol was used, given in graduated weekly doses of 10 per cent PDC, beginning with 0.05 ml. The highest practical intramuscular dose was 1.0 ml of the 10 per cent concentration. Alum-precipitated pyridine extracts were used in moderately sensitive persons according to the regular schedule. There was no reduction in the patch test response in any of these individuals. Patch test with one to five aqua ivy on four highly sensitive subjects produced no reaction. About 500 subjects participated in oral prophylaxis with PDC. Maximal hyposensitization required 3500 to 4000 mg. Hyposensitization lasted for about four to six weeks after oral prophylaxis, and about eight to ten weeks after intramuscular treatment. Since various dosage schedules were used, cutaneous, mucous membrane and systemic reactions were noted in considerable number with high dosages. Eosinophilia of 20 to 59 per cent was noted during courses of hyposensitization. Cortisone, 25 to 100 mg, given with each injection, suppressed local reactions. Very little is understood about mechanisms of hyposensitization. Leukocytes from three hyposensitized donors readily transferred PDC sensitivity to three originally non-sensitive subjects. "Hardening" has been proved with dermatitis producing patch tests over a period of many months. The opinion is expressed that intra-

muscular prophylaxis with PDC, 10 per cent in sesame oil, was impractical. Oral prophylaxis is the preferred route. Hyposensitization is temporary and the original sensitivity is gradually regained within six to ten months. A more novel approach to poison ivy prophylaxis is reported by Keil.[92] Wheals were made in the skin with small doses of synthetic 3-n-pentadecylcatechol. A course of treatment consisted of six consecutive wheals made at weekly intervals. Twenty courses were followed by complete freedom from subsequent attacks of poison ivy dermatitis. Fewer courses were followed either by complete failure or transient attacks.

Kligman[97] has recently reported extensive studies of the entire subject of Rhus dermatitis, as well as the background of hyposensitization with specific antigens for this common disorder. It was found that cashew nut shell oil, in a concentration of 10 per cent in ethyl alcohol, could accomplish successful hyposensitization of the Rhus sensitive person. The cashew tree is extensively cultivated in Brazil and India because of the edibility of the fruit. Although the nut is prized as an important commercial product, the shell has only recently been of value. The oil in the shell is used in a host of manufactured products, such as insulating varnishes, floor tiles, brake linings, typewriter rolls and cold-setting cements. The fully "cured" resins are harmless, and millions of pounds of crude oil are imported annually into the United States. The allergenic constituents of Japanese lac, poison ivy and the cashew tree have been accurately defined chemically through the researches of Dawson and his collaborators at Columbia University, and have been previously outlined in these reviews. Hyposensitization is accomplished orally, using one drop daily for the first week, two drops daily for the second week, three drops daily for the third week, and four drops daily for the fourth week, thereafter increasing one drop every four days to the total of twenty drops daily and continuing at this final dose until a total of 35 ml has been consumed. Occasional skin eruptions and inflammatory reactions of the oral mucous membrane occurred, but these were never serious. In this series, fifteen Rhus sensitive adult males were used, and the dosage plan outlined for cashew nut shell oil proved about equal to PDC in hyposensitizing efficacy.

Langs and Strauss[101] report oral prophylaxis against poison ivy dermatitis with aqua ivy tablets; 142 men of the United States Coast Guard were included in this study. These men worked at clearing brush along the banks of the Mississippi river and its tributaries, and the period of observation and tablet ingestion was from April 23, 1956, to November 1, 1956. Two groups were formed in a random fashion to qualify the study for a double-blind control study. The incidence of poison ivy dermatitis in the treated patients (sixty-five men) after six weeks of ivy tablet ingestion was 6 per cent, and that of the control group (fifty-seven men) was 21 per cent. A further experiment done in 1957 indicated that aqua ivy tablets afforded complete protection against poison ivy dermatitis for 88

per cent of subjects with a past history of dermatitis after they had taken the tablet for six weeks. Fifteen men with a past history of poison ivy dermatitis were patch tested, and of these, thirteen gave a negative patch test. These men had been treated with aqua ivy tablets. One of the drawbacks of the experimental procedure was the lack of a physician's confirmation of the diagnosis of poison ivy dermatitis in 75 per cent of the cases. Side reactions were relatively absent, and toxicity completely absent in these experiments with aqua ivy tablets. While Kligman[95] believes that there is no practical local measure that will adequately protect against field exposures to poison ivy, Gross[71] orally fed 455 subjects who were sensitive to poison ivy, a stable extract of fresh poison ivy leaves and stems. This was prophylactic treatment, giving small daily doses for six weeks before the poison ivy season. During the season, maintenance doses at longer intervals were used. In the treated patients, 77 per cent of the subjects were either free of ivy dermatitis or had minimal attacks. A 1 to 4 dilution of the tincture of jewel weed was used by Lipton[107] in the treatment of Rhus dermatitis. One hundred and fifteen patients were used in this clinical trial; one group was treated with jewel weed, and on other areas, the well-known menthol-calamine mixtures, and in the other group, topical therapy was used. It was concluded that jewel weed was an effective local treatment for Rhus dermatitis; symptoms were controlled within two to three days after therapy was begun.

Cross-sensitization in the members of the sumac family, anacardiaceae, was studied by Howell.[77] There is a close botanical and immunological relationship among poison ivy, poison oak, poison sumac, cashew nut shell liquid, Bhilawanol, Bhilawanut and Bhilawana tree and the Japanese lacquer tree. Twenty-three subjects were studied, and tables were presented to show cross-sensitization. A solution of 0.1 per cent 3-n-pentadecylcatechol produced negative reactions in thirty-four of fifty individuals tested. It was thought that the extract was too weak. This extract represents the underlying chemical structure of the antigen found in the entire sumac family. Interesting case reports are presented demonstrating sensitization to the dhobie marking fluid and cashew nut sensitization.

Fromer and Jenkins[62] reviewed their experience with ragweed oil dermatitis. This is a seasonal dermatitis that occurs in males over forty years of age who are outdoor workers. As a rule, the exposed areas are involved. Other sensitivities may prolong the dermatitis but early in its course the skin usually clears soon after the first killing frost. Patients do not have a background of asthma or ragweed hay fever. Positive patch tests are obtained with a dilution of ragweed oil, 1 to 1000 solution. There are few false-positive or false-negative tests. Treatment consists of avoidance of contact with the plant. Injection therapy with ragweed oil is reasonably successful in 80 per cent of patients so treated. Oral hyposensitization may also be achieved with ragweed oleoresin.

Matz and Blank[117] report the case of a twenty-two-year-old woman who

developed contact dermatitis from Thermofax paper. The lesions were on the medial aspect of the right forearm, the front of the neck and the right side of the face. About two weeks later the eruption had extended to the palms and the sides of the fingers. It was determined that the eruption was the result of contact with Thermofax paper. Concentrations of 0.01 per cent, 0.1 per cent and 1.0 per cent of 4-tertiary butyl catechol in petrolatum were applied as standard patch tests. All areas tested showed erythematous responses, and the 1.0 per cent strength was followed by a pruritic and edematous reaction. Control studies were made with coded papers to prove the sensitivity to the catechol. Thermofax paper no longer contains this chemical. This catechol (4-tertiary butyl catechol) is used in addition in the manufacture of rubber, the production of paints, and the preparation of gasoline and petroleum products, as well as in the manufacture of plastics. It is structurally related to the catechols in the ivy family. Hasegawa[72] and others report contact dermatitis due to Thermofax copy paper. Previous reports have appeared from many parts of the country. In the case report presented, a severe dermatitis of the face, arms, dorsum of the hands and wrists might have been caused by some injections of penicillin. However, the patient remembered that he had used Thermofax duplicating paper for several weeks before the onset of the dermatitis. It is to be remembered that the allergenic component in Thermofax paper is said to be a tertiary butyl catechol compound and that this preparation has probably been discontinued in the more modern duplicating papers.

Ayres and Ayres[4] report contact dermatitis from Philodendron, a plant in current vogue for interior decoration and for patios, especially in the warmer sections of this country. The genus Philodendron is one of approximately 100 genera in the family Araceae, which includes such plants as the common calla lily, and most members of this family come from tropical areas. A series of twelve patients, most of them housewives, with contact dermatitis from *Philodendron cordatum* is presented. Philodendron dermatitis is discussed by Dorsey.[44] While this is a rare sensitizer in actual use, workers in commercial greenhouses may become involved with this plant. It is felt that the toxic or allergic principle of Philodendron is water-soluble, and workers in the field become involved with wet leaves or with cut leaves and stems many times daily.

In response to a question on celery contact dermatitis, the consultant stated that eczematous dermatitis caused by contact with celery was reported in 1926 in the French dermatologic literature.[155] The essential oil of the plant was incriminated. Limonene, present in celery, is also common to orange, lemon, bergamot, caraway and dill. The large bullae found in workers in Michigan correlate with an eczematous process of contact origin. It is also necessary to consider sprays with fungicides or pesticides. An additional factor in celery dermatitis[210] may be due to the presence of photodynamically active furocumarines in celery, as well as in

parsnips. Studies at the University of Oregon School of Medicine have recently demonstrated significant amounts of psoralens in celery. Field workers should be advised to avoid skin contact with the essential oil, and direct solar exposure.

Algerian ivy, largely cultivated in California, was a cause of dermatitis in twelve patients described by Dorsey.[45] The eruption occurred within twenty-four to forty-eight hours after trimming the plant. The characteristics of the eruption are similar to those produced by poison oak, but are milder. Effective results were obtained in this series by the administration of corticosteroids. A daily dose of 20 mg of prednisone was usually sufficient. Topical treatment was not effective.

The diagnosis of shoe dermatitis depends on the history, the clinical appearance, positive patch test reactions to shoe material, and the patient's ability to wear proper substitute shoes without dermatitis, according to Fisher.[57] Patients with a suspected shoe dermatitis are patch tested with a screening tray which includes materials in rubber thermoplastic box-toe material. Substitute shoes which can be used for patients who have developed hypersensitivity to either the agents in thermoplastic box-toe material, or to potassium dichromate, paraphenylenediamine, or nickel sulfate are described. If patients are allergic to the chrome in leather, vegetable-tanned shoes are available. The reviewer notes that this is a basic article, and while the author is in fundamental disagreement with Morris on the nature of chrome used in the patch test, this problem will probably be resolved in time.

A comprehensive review of the problem of hand eczema is reported by Sullivan and Farber,[204] and a classification is presented under the following headings: contact eczema, infected eczema, mycotic eczema, "id" eruptions, nummular eczema, pompholyx, atopic dermatitis, food allergies, inhalant allergies, and miscellaneous hand eczemas. Some of the causes in hand eczemas overlap so that, in nummular eczema, one must consider nutrition, infection asteatosis, atopy, trauma, dermatitis venenata, and bacterial allergy. The opinion is that food allergy represents an uncommon cause of dermatitis of the hands. Some of the newer concepts include the association of inhalant allergens and dermatitis (Jillson and Piper, 1955).

Lithographer's dermatitis is reported by Levin and others[104] who made a survey of the industry. One hundred men representing all job categories within the industry were examined. Seventy-six men with active dermatitis, either at the time or in the past, were compared with twenty-four men free from dermatitis. In modern lithography, the "deep-etch" process requires the use of kerosene; turpentine; a turpentine substitute containing pine oil, castor oil, ester gum and naphtha; phosphoric, chromic and hydrochloric acids; gum arabic; potassium and ammonium dichromate; benzene; inks; asphaltum, and varnish remover. Other agents must also be used. In this series 78.3 per cent of the patients with contact dermatitis showed positive reactions to one or more of the occupational contactants. An

excellent list of patch tests used in lithography with proper concentrations and diluents is appended. Pressmen in this industry are exposed to lipid solvents, and it was thought that this factor contributed to the pathogenesis of sensitization to chromate, the most common allergen. Kile and Quigley[93] studied the incidence of skin eruptions in uranium workers. Of 174 patients seen by the dermatologist, thirty-six had contact dermatitis, twenty eczematoid dermatitis, twenty-two fungal infections, and fifteen asteatosis. An elaborate plan is followed to keep the workers from excessive chemical or radiologic exposure in the uranium plant. Two showers daily resulted in a certain amount of dryness of the skin, which may have predisposed to chemical sensitization. Holtzman[76] described a four-year-old girl with a papulovesicular eruption associated with pruritus which was limited to the palms of both hands from the wrists to the fingertips. Duration was two weeks and seemed to coincide with the purchase of a "hula hoop." Scrapings of the plastic material from the surface of three different colored hoops were used as patch tests, and the results in forty-eight hours were positive at all three sites. An aluminum hoop was substituted.

Knight[98] made a five and one-half year survey of experience with dermatitis in an ammunition plant. It was found that there was a steady drop in the incidence of dermatitis from seventy-five cases per one million man hours in 1951 to seventeen cases in 1957. This was accomplished by careful selection of workers so that no one with an active skin eruption was admitted to the plant. Candidates who had acne, eczema, dermatophytosis or psoriasis were not allowed in the manufacturing area. Annual examinations were carried out, and prompt attention to beginning dermatoses was afforded each employee. In addition, the general industrial hygiene was carefully followed.

In a discussion of the etiologic factors for the causation of pruritus ani and vulvae, Osborne and Stoll[139] note that next to primary irritation, contact dermatitis may be the most common cause of pruritus of the anogenital area. The chief allergenic substances include local medication, toilet tissues, suppositories, enema and douche nozzles, contraceptives, resin finishes on fabrics, drugs taken by mouth, nail lacquer, deodorants, plant oleoresins, and some foods. Some food sensitivities were confirmed with patch tests, some with intradermal tests, and others by use of elimination diets. It is believed that contact dermatitis caused by oleoresins in certain foods, and particularly condiments, offers a fruitful field for investigation. Eleven cases of anogenital pruritus caused by specific hypersensitivity to oleoresins of condiments are recorded.

In response to a question on formaldehyde hazard, the consultant[150] stated that urea formaldehyde resins have long been used in industry. Thermosetting glue in laminating wood production requires the presence of this agent. Contact dermatitis to unpolymerized resins occurs. These agents are also used in the garment industry, but are not a problem if polymerization is complete. In response to the question of allergic reaction

to topical applications of various types of silver protein solutions, the consultant stated that the danger of sensitization to silver salts appears to be remote.[160] In one case reported by Criep (1943), sneezing, blockage, rhinorrhea and wheezing developed in the course of local treatment with a mild silver protein in the nose. Scratch tests and passive transfer reactions gave positive results. Borelli[25] investigated preventive measures against skin injuries from cold wave developers. Cold wave compounds cause swelling and loosening of the stratum corneum and also have a non-specific effect of the alkali which they contain. These effects are increased by thioglycol and alkali. To prevent a keratolytic effect, hairdressers have been advised to rinse with peroxide and an acid rinsing solution after the use of these agents. In addition, application of fatty ointments seems to be effective in protecting the skin of the hands of the operators. It may take two or three applications for each client.

Several cases of lipstick cheilitis were studied in England by Calnan and Sarkany.[34] As has been noted for many years in the American literature, the fluorescein dyes are the important agents which produce reactions of hypersensitivity. These indelible dyes contain halogenated derivatives of fluorescein (Eosin) and apparently this agent combines with the keratin of the stratum corneum. Indelible lipsticks, which are the ones in common use, are incriminated in lipstick cheilitis. These patients, however, can use fluorescein-free lipsticks. It is important to remember that false-negative patch tests may be seen in suspected cases because too little of the allergen gets through the stratum corneum. Clinical evidence, therefore, is most important. The formaldehyde-sulfonamide resin in nail lacquer is chiefly responsible for the dermatitis frequently seen on the eyelids, face and neck. Stritzler[201] found a group of four patients with patchy contact dermatitis of the face and neck which was proved to be due to pearly nail lacquer. This contains guanine and the material is derived from the fish scales of sardines. All of the patients had eaten sardines with no obvious reactions, but none of them had been in contact with sardine scales or sardine skins previously. In response to a question regarding a patient who was found to be allergic to deodorants containing aluminum or hexachlorophene, the consultant[164] stated that sensitivities to these agents rule out the use of most commercial deodorants. The patient was urged to try sodium bicarbonate as a substitute, or request a formulation from one of the manufacturers of hypoallergenic cosmetics. A review of essential data on perfume dermatitis was presented by Klarmann.[94] In the discussion of perfume sensitivity data, the early work on berloque dermatitis, which is a photosensitization of bergamot oil in perfumes, was noted. Subsequently, other investigators have shown photosensitizing substances, such as the psoralens, which are present in a variety of natural essential oils, including bergamot oil, other citrus oils, oil of neroli, oil of lavender, and a group of essential oils, many of which do not need a light source to sensitize. The author suggests that perfume

dermatitis may be a fruitful field for further exploration in the production of dermatitis.

Malten[113] studied the effect of sensitivity to paratertiary butylphenol in shoe adhesive. This preparation is a cement which is involved in binding the outer and inner soles, and lesions have been seen in workers who come in direct contact with the preparation. The cement contains a neoprene rubber, a resin that contains the agent paratertiary butylphenol formaldehyde, and an unknown catalyst, as well as binders of zinc and magnesium oxides and other solvents. The chemical reacted in ten patients who also showed reactions to phenol formaldehyde resin. General measures to prevent the increased incidence of dermatitis from the cement are outlined by the author. Burckhardt[33] studied two patients suffering from a dermatitis on the light exposed areas of the face, hands, neck and forearms. This was apparently caused by a detergent that contained optical brightening agents which are brighteners. These agents have been added to detergents, white paper and textiles, and physically change invisible ultraviolet light into visible blue light. These agents are chemically related to sulfonamides. By exposing the patient to the detergent which contained the optical brightening agent, the author was able to produce a recurrence in areas exposed to the Kromayer lamp. In response to a question concerning the chemicals used in rendering cotton fabrics "drip dry," the consultant[159] stated that certain resinates such as melamine formaldehyde and urea formaldehyde are contained in some of the "drip-dry" chemicals now in use. No reports on skin sensitization caused by these chemicals have appeared, but it is conceivable that dermatitis may occur and cross-sensitization might also occur. In response to a question regarding dermatitis after exposure to spun glass, the consultant[161] stated that spun glass is a pruritogenic substance capable of causing a dermatitis. An eruption resulting from use of this agent, however, would not recur every two to four weeks without further exposure, as noted in the problem presented. Other suggestions were to make a morphologic diagnosis. Herpes simplex should be considered, as well as other suspicious contactants from the patient's environment.

Birmingham[17] is of the opinion that when a dermatitis is caused by detergents, it follows a low grade primary irritation or specific sensitization, or at times, a combination of both. Many investigators believe that these dermatoses occur on the basis of primary low grade irritation. Patch tests to soaps and detergents have shown that specific sensitization to these substances is uncommon. The mechanism probably consists in the removal of surface lipids and water loss from keratin which is facilitated by the primary irritant effect. Other factors, such as temperature and humidity, also play a role, especially in recurrences of hand eczema. The reviewer notes that the problem of hand eczema is further confused by a series of patients brought into the hospital with this disorder who continue to use soap and detergents while in the hospital, but their hand dermatitis regularly improves under these conditions.

Baer and others[8] describe allergic eczematous sensitivity to aminophylline in a fifty-eight-year-old pharmacist. He was first seen in 1953 when he complained of a severe eczematous, erythematous, edematous, scaling eruption over the scalp, face, arms and lower extremities. It was learned that he had flare-ups subsequent to filling capsules containing papaverine, amobarbital (Amytal) and aminophylline. Patch testing with ethylenediamine dihydrochloride, as is, produced a 5-plus reaction, and the same drug in 1 per cent aqueous solution produced a 3-plus reaction. Theophylline, as is, and theophylline, 1 per cent in 70 per cent alcohol, gave negative results. In the past four years the patient has had no recurrence since he has avoided all forms of aminophylline. Ethylenediamine is employed in various organic syntheses for the preparation of dyes, inhibitors, rubber accelerators, fungicides, synthetic waxes, resins, insecticides, asphalt wetting agents, and certain pharmaceuticals. In response to a question about the occurrence of ear eczema in repeated pregnancies, the consultant[152] stated that hormonal influences in various forms of eczema are well known. Included in this group are aggravation during menstruation, improvement or aggravation during pregnancy and the frequent origin or continuation of contact dermatitis during the climacteric. It is not known whether any hormonal imbalance may account for these occurrences.

Practical advice in the management of contact dermatitis is recorded by Morris.[130] For acute dermatitis with excessive amount of pus, a combination of local compresses is suggested. This consists of the use of sodium hypochlorite solution, using one tablespoon to a quart of cold water. Soaking time is two to three minutes. Parts are rinsed with cool water, and this is followed by Dalibour water soaks. The prescription for Dalibour water is copper sulfate 5.0; zinc sulfate 15.0; water to make 120.0 This is diluted one teaspoon to a quart of water. Ointments and salves are avoided during the acute phase.

The prevention of occupational dermatitis with special reference to barrier substances was investigated by Porter.[148] He devised a number of tests designed to determine the usefulness of a number of barrier creams available commercially. The weakest point of most of the barrier creams tested has been the poor resilience of the film. Some creams were so adherent that they could not be removed except by very hard scrubbing. This process made the hands sore and in some instances was liable to give rise to dermatitis. A mixture of neutral sulfonated castor oil and a wetting agent was found to be the best agent for removing this type of barrier cream. Improved conditions for workers would involve insuring that clothing is kept clean and uncontaminated; adequate provision of efficient and well-designed protective clothing; alteration of machinery and materials when necessary; provision whenever possible of mechanical means of handling irritants and sensitizers; installation of appliances to remove fumes and dust, and sterilization of oil and materials that are used repeatedly in the manufacturing process. It was the opinion

that prevention of dermatitis must lie elsewhere than in the use of barrier substances unless drastic changes are made in the preparations now available. The study was undertaken in England with special reference to the leather industry. The various barrier creams available for protection of the skin against sensitizers and common irritants are discussed by Sneddon.[193] Their effectiveness is controversial. Their use allows the skin to be cleansed more easily during and after working hours. They do not offer adequate protection against prolonged contact with alkaline solutions or industrial solvents. It is possible that barrier creams may facilitate the production of dermatitis by allowing penetration of sensitizers into the deeper layers of the skin. Barrier creams with silicone have been recommended for diaper rashes, protection of the skin around colostomy openings, and for the prevention of bed sores in debilitated patients. Barrier creams for light sensitivity eruptions have also been useful in chronic discoid lupus erythematosus and xeroderma pigmentosum.

In discussing eczema, Bowers[26] believes that the friendly touch often accomplishes a great deal in the office management of patients. In virtually every case of eczema, it is important to remind the patient that the condition is not infectious and must not be subjected to unskilled therapeutic trials. In addition, the physician should say specifically that it is nobody's fault and that it is not a venereal disease. These homely assurances calm the patient's fears. What he really fears is that we may have recognized something about his past and that we are withholding this information from him. Lackenbacher[100] used polaramine, either in a 2 mg tablet, or 6 mg repetab, in thirty-six patients with contact dermatitis and found that the itching was controlled in twenty four, well controlled in nine, and fairly well controlled in three. Based on 200 case records, Rogers[174] finds that next to allergic rhinitis, antihistamines are most commonly effective in the management of contact dermatitis and chronic urticaria. Some form of Chlortrimeton or Pyribenzamine is useful for daytime use. Benadryl and Phenergan were also used extensively. Sixty antihistaminic agents are available and often it is useful to change from one preparation to another if adequate dosage has not afforded symptomatic control.

ATOPIC DERMATITIS

Results of scratch tests in 114 infants and children with eczema were analyzed by Ratner and Collins-Williams.[169] About 97 per cent of the entire group showed one or more reactions. A higher percentage of food reactions was noted in infants whereas a higher incidence of reaction to inhalants was found in older children. Fifty per cent of children with uncomplicated eczema had pollen reactions while only 24 per cent of the infants reacted to pollens. Careful studies were necessary as the infant grew older to disclose new pollen and inhalant sensitivities. The allergens showing the greatest number of positive reactions in infancy were egg, vegetables, inhalants, fish, fruits, meats, nuts, wheat, condi-

ments, and milk. Among children however the vegetables were followed by inhalants, fish, fruits, condiments, egg, nuts, bacterials, cereals and wheat, in that order. Food sensitivity, while frequent, must be correlated with clinical observation.

A short review of the experience with patients with atopic dermatitis over a period of eight years is recorded by Grayson and Shair.[69] Charts of 106 individuals were taken at random from the files and reviewed. Emotional disturbances were found to aggravate a pre-existing eruption, but special psychiatric treatment did not seem to be necessary. Fifty-one patients had no known associated allergic stigmata. The earlier the onset of the dermatitis, the better the prognosis for freedom of the eruption in adult life. It is the opinion that the best management consists of (a) topical medication, (b) radiation (grenz ray and x-ray) and (c) oral and parenteral medication. Hyposensitization was thought to be of limited value for the cutaneous eruption. In a review of fifty records, only twelve had routinely had intracutaneous tests.

Morris[127] agrees that foods play an important role in the etiology of atopic dermatitis, and this is true especially in infancy. Gastrointestinal disturbances following the ingestion of a food suggest that that particular food be avoided. Eggs, wheat and milk are the most common offenders. The author makes use of diet diaries and questionnaires and considers botanical relationships in the management of diet diaries. Inhalants play a role in older children and bacterial involvement indicates a high degree of susceptibility of atopic individuals. Staphylococcus toxoid frequently is helpful in such cases.

Simonart[189] develops the thesis that conditioning is the dominant role in responses of individuals with dermatologic allergy. Conditioning cannot be prevented since responses depend on haphazard circumstances so that conflict at later times develops. What is perfectly acceptable at the age of two years is repulsive at twelve, and may be attractive at the age of twenty two. Clinical examples are presented. It is the opinion that the nonprofessional psychiatrist should not practice definitive psychotherapy. Instead, a careful history of the educational, marital, occupational chronology along with the chronology of manifestations of autonomic nervous system disorders and of emotional evolution and conflicts will give the dermatologist some insight as to possible causal relationships.

In answer to a question on atopic dermatitis and climate, the consultant[156] stated that climatological therapy is frequently helpful, sometimes to the point of complete disappearance of the skin disorder. Such patients sometimes do well in southern Florida or California. Denver, Colorado, is suitable during the warm months of the year, but recurrences might be noted during the cold winter season. Climatological therapy is not always successful.

Reynolds and Joos[172] establish a number of steps which are recom-

mended for the prophylaxis of eczema vaccinatum. It is the opinion that no child with atopic eczema or other skin disease should be vaccinated. No child should be vaccinated if any member of his family has eczema or other skin disorders. Parents of children with eczema should be notified about the dangers of vaccination contact. An atopic child who has been in contact with another sibling recently vaccinated should be isolated for twenty-one days. It is suggested that eczema vaccinatum be a reportable disease, and that patients recently vaccinated be excluded from pediatric wards where there are patients with atopic eczema. Babies as young as two months of age may be vaccinated, especially those with strong allergic family histories.

The query is raised[165] regarding a seventeen-year-old boy who has had atopic eczema all of his life. He plans to tour Europe and requires a smallpox vaccination. This was successfully accomplished when he was six years old, but two dermatologists have advised against giving him another vaccination. The consultant stated that, according to the laws of the United States, he must be vaccinated against smallpox if he is to be in Europe. It was suggested that if the condition was relatively clear and if there were no active areas of dermatitis, the patient could be vaccinated.

Meenan[121] discusses the prognosis of infantile eczema. This usually commences as an erythematous patch on the cheeks of the baby at about three months of age. There is usually extension with remissions and exacerbations until the child is between eighteen months and two years, when the eruption becomes papular and scaly with less oozing. At about this time, too, most cases will clear. There is a familial or hereditary background of allergic disorders, especially in cases of flexural eczema. Present methods of treatment of infantile eczema are not very effective. Questionnaires were mailed to the parents of children who had been treated for infantile eczema in the Children's Hospital, Dublin, from 1932 to 1945; more than 50 per cent replied. Forty-two cases were available for analysis, of which twenty-three were males and nineteen females. The eczema cleared at about age two in fifteen children, around the age of eight years in ten children, between the ages of fifteen and twenty-one in four patients, and in thirteen the eczema persisted. Asthma developed in eleven of forty-two children.

The relationship of the psyche to atopic dermatitis is critically reviewed by Rostenberg.[180] Much of the confusion in this field stems from the difficulty with the concept of causal relationships. For example, it is important in ivy dermatitis to have contact with the ivy as an essential component in the picture. Posing this type of logic, one could then ask whether emotional influences need be a necessary part of atopic dermatitis. Most physicians would be inclined to agree that an interrelation exists but the various formulations are viewed with suspicion. Some writers have used the concept of conversion, which postulates that repressed energy connected with a frustration of basic drives is converted into the functional

symptoms of bodily disease. This is difficult to prove scientifically. Studies of personality profiles show a high statistical correlation between certain diseases and certain personality types; however, these studies have never been controlled. The work of Greenhill and Finesinger is quoted because attempts were made to control atopic dermatitis, lupus erythematosus, psychoneurosis and normal controls in this particular study. Many of the findings in this personality profile have been doubted by other investigators. Rostenberg finds little to support the maternal personality profile in relationship to the child with atopic dermatitis, and most of the writing by psychiatrists is termed "an inferential hypothesis stemming from the analytic interpretation of the emotional states in people with various somatic alterations." This statement, while directed to the findings of one particular psychiatrist, sums up the opinion of Rostenberg. While he is sympathetic toward the psychosomatic concept of atopic dermatitis, he thinks that the emotional factors are only one facet of a dynamic interplay of factors which produce itching in a genetically determined soil. The evidence does not justify giving the psychosomatic aspect undue importance and if so, deserves (according to the author) Mencken's derisive comment: "There is a solution for every human problem—neat, plausible, and wrong."

Lipman[106] evaluated Dimetane in five patients with atopic dermatitis. The response in control of itching and symptoms was good in two, fair in one, and poor in two. The drug was as effective as Chlor-Trimeton in the treatment of primary allergic syndromes and seemed to have fewer side effects. Lackenbacher[100] used Polaramine, either in a 2 mg tablet or 6 mg repetab, in eight patients with atopic eczema. Control of itching was excellent in five, good in two, and fair in one. Trimeprazine (Temaril), a phenothiazine derivative, was used by Williams[222] for ninety patients with severe pruritus associated with acute and chronic dermatoses. Relief from pruritus was obtained in 75.5 per cent of cases with a loading dose of 10 mg daily. Side effects were minimal. My experience with Temaril suggests that relief of itching may be very irregular and while it is worth a trial when itching is refractory to other measures, it cannot be depended upon regularly to suppress itching. In addition, since it is a phenothiazine, the possibility of a production of photosensitivity must be considered.

Murrell and Taylor[133] investigated the cutaneous reaction to nicotinic acid (niacin)-furfuryl because of its known failure to react in patients with rheumatoid arthritis and atopic dermatitis. If a small amount of 5 per cent of this agent in lanolin petrolatum base is rubbed in or simply laid on the skin of normal persons for twenty to thirty minutes, over 95 per cent show an erythema with or without edema. The nicotinic acid-furfuryl reaction was not altered experimentally by antihistamines or coenzymes I. Steroids given internally do not directly affect the reactions; they do not alter the cutaneous response when applied locally. The mechanisms

and interpretations of the blanch reaction in atopic dermatitis is still unexplained.

Hasselmann[73] evaluated 2600 blood serum electrophoreses in various dermatoses, including over 800 atopic and other eczemas. Albumin was significantly decreased, gamma globulin significantly increased and beta globulin questionably increased in atopic eczema. Various forms of eczema showed marked hypo-albuminemia and increase of alpha, beta and gamma globulin.

In his "Fourth Review of Microbial Allergy," Blatt[22] notes that the role of infections in atopic dermatitis is still doubtful. Positive skin tests to bacterial allergens cannot be reliably evaluated. "A guarded view must, therefore, be taken of bacterial hypersensitiveness." A goodly number of useful references and their abstracts may be read with profit in this review. Microbial allergy and its relationship to various collagen disorders, vascular disorders and specific microbial infections are summarized. Blatt quoted Rajka,[167] an excellent European worker, who noted that bacterial infection and anacidity or hypoacidity were present in a number of patients with physical allergy to a degree that would warrant the speculation of the double role of infection plus physical factors in this disorder.

URTICARIA AND ANGIONEUROTIC EDEMA

The erythema which accompanies many cutaneous inflammatory processes may be due to axon reflex vasodilatation; however, the chemical mediator of this vascular response remains unidentified. Lorincz and Pearson[109] undertook a number of studies on axon reflex vasodilatation and cholingeric urticaria, using two patients who suffered from cholinergic urticaria. In this condition the lesions, clinically, are typically tiny 2 to 4 mm wheals, usually surrounded by bright erythema. The usual stimuli for the release of acetylcholine which mediates this response are heat, exercise or emotional tension. A number of agents were used in this study: acetylcholine iontophoresis; nicotine picrate, 1 to 50,000—1 to 100,000 intradermally; intradermal atropine sulfate, 1 to 25,000—1 to 250,000, and prostigmin, 1 to 10,000—1 to 40,000. It is emphasized that all testing in patients with cholinergic urticaria should be avoided during a refractory period which may last four hours after severe outbreaks of the lesions. Study of the satellite wheals in areas in which axon reflex sweating has been elicited provides a more easily interpreted test phenomenon than local whealing to injections of cholinergic drugs. The question of the neurohumoral mediator of axon reflex vasodilatation indicates that this mediator is not acetylcholine, histamine or serotonin. Sweating induced in two patients with cholinergic urticaria did not show lesions of the disorder such as were precipitated by activation of the cholingeric innervation to the sweat glands. Rorsman[176] studied basophil leukocytes in urticaria, asthma, and atopic dermatitis since some of the properties of basophil leukocytes

and tissue mast cells are similar. Basophils were decreased in most cases of urticaria and in some these cells completely disappeared. Blood histamine also decreased in patients with urticaria. In three patients with cold urticaria, however, histamine concentrations and basophil counts were normal. While Bersani[15] encountered normal basophil counts in allergic contact dermatitis as reported by Baer and Witten, further studies showed lower basophil counts in atopic dermatitis. It was felt that the series was too small to make these differences significant.

Another form of urticaria due to physical agents is solar urticaria. Brunsting and Epstein[31] describe the two forms due to wave lengths in the visible spectrum from 4000 to 5000 angstroms chiefly in the blue-violet range and that type which is due to wave lengths shorter than 3700 angstroms. The clinical manifestations of both types are similar in that pruritus and erythema are seen together with a wheal when the skin is exposed to the suitable wave length. The reaction persists from minutes to one hour or more. Passive transfer of sensitivity occurs with wave lengths shorter than 3700 angstroms. Treatment is fairly successful with the use of barrier or protective creams, antimalarials and antihistamines. Magnus and Porter[111] studied a case of urticaria solaris by means of a monochromator. With this technique the investigators were able to select wave bands from any region of the ultraviolet range down to about 240 mu. In this patient erythema developed early at 290, 300 and 310 mu, it appeared within one or two minutes and always preceded the formation of wheals. Following exposure to the threshold dose, or a little more, wheals took up to ten minutes to develop fully. Wheals lasted about thirty minutes and when they subsided they were followed by a distinct erythema for the same length of time or longer. The patient reported that exposure to bright sunlight for a few minutes causes a wheal and sunburn does not appear. Violet, orange, red and infrared light failed to produce a wheal in this patient. However, urticaria was caused by exposure to blue and green light. The patient stated that the disease had become much less severe over the past five years. It is suggested that early erythema and whealing may be due to different mechanisms. Lewis had shown that vascular dilatation and increased permeability of the capillaries were recognized some time ago as separate entities. The early erythema may be caused by a histamine-like substance formed by the action of light on epidermal cells. This reaches the blood vessels of the dermis by diffusion. The relationship between early erythema and whealing, as well as the photosensitization mechanism, is discussed briefly.

Nelson[137] discusses cold urticaria in a case presentation of a Negro woman, aged forty-four, who complained of hives, following exposure to cold, of ten months' duration. Urticaria was first noted when she touched an icy object. Later, burning sensations developed in the mouth and tongue whenever she ate or drank cold food. Finally, any contact with cold resulted in so much edema of exposed parts that the patient had been

unable to leave the house for several months. Laboratory studies were within normal limits. Application of ice to the skin was followed by the development of a typical hive. Intradermal injections of mecholyl chloride failed to produce pruritus or urticaria, but an injection of histamine reproduced the patient's symptoms. These were easily terminated by an injection of aqueous epinephrine. Passive transfer (P.K. test) was successfully accomplished. Cold agglutinin test gave negative results. Rosenbach test for cold hemoglobinuria was negative. The patient was given 1-benzyl, 2-methyl, 5-methoxy tryptamine hydrochloride (B.A.S. Merck, a specific antimetabolite for serotonin) in doses of 400 mg daily. This produced at least a 75 per cent increase in her ability to tolerate cold. Because of excessive sleepiness the dose was lowered to 100 mg daily. In discussion, it was stated that perhaps serotonin may play a role in urticaria in man. The immediate (anaphylactic) type of hypersenstivity in the mouse is mediated by serotonin, not histamine, and it may be that man reacts more like a mouse than a guinea pig. Urticarial lesions have not been produced experimentally with either serotonin or acetylcholine in man. Rajka and Vincze[168] report the rare instance of urticaria and erythema due to the physical agents of both cold and heat in the same patient. The exact pathogenesis has not been determined. In favor of the allergic mechanism was the occurrence of sudden attacks associated with itching and a refractory phase which appeared after positive tests. There were, however, negative passive transfer and diminished response during prolonged drug-induced sleep which were thought to be factors that denied an allergic mechanism.

Urticarial reactions after x-ray treatments are not common. Weber[218] studied the reactions of a man, sixty-nine years of age, who was given 500 roentgens for the treatment of basal cell epitheliomas on the face and trunk. Redness and whealed lesions appeared over the treated areas six hours later. Serum withdrawn from a cantharides blister of the patient successfully transferred the urticaria-like eruption to a recipient who was likewise treated with 500 r. In this instance, the important factor was the total dose of 500 r rather than any specific voltage-induced wave length.

In recent years a number of insects have been accepted as playing a causative role in the production of papular urticaria. Flies, chiggers, mosquitoes and bedbugs have been incriminated. Yaffee[224] presents the case histories of two females, ages twenty-four and seven, who presented an eruption on the trunk consisting of 5 mm to 1 cm urticarial, papular, conical-shaped lesions and excoriated areas. As in other cases, the generous use of insecticides in the household resulted in the control of the disease. For some years Waldbott[216] has been interested in the toxic and allergic effects of the ingestion of fluoride which in certain communities is added to the drinking water in an attempt to control tooth decay in the population. In addition to a number of neurologic and gas-

trointestinal symptoms, the author describes recurrent urticaria in six women who drank fluorinated water. Urticaria could be reproduced readily by ingestion of test quantities of fluoride water. Skin tests were inconclusive. Santos and Unger[181] described a severe allergic reaction to pignolia nut in a patient aged thirty-two following the ingestion of a piece of candy containing pine nuts. The seed of this tree is native to Italy, Spain and Turkey, and yearly about 200,000 pounds of these nuts are imported into the United States for ingestion in a number of forms. The nuts are mixed in sausages or cakes and cookies and, as in this case, in candy. The patient required hospitalization and vigorous treatment for control of the attack.

Most allergists have seen and treated patients with urticaria pigmentosa. It has been reported that Benadryl offers some of these patients a certain amount of symptomatic relief. Treatment, however, is generally unsatisfactory. Baer and others[7] studied the effect of reserpine on urticaria pigmentosa. In the histology of the lesions in man, many mast cells are found. On the basis that reserpine either neutralizes or diminishes the number of granules in mast cells in animals, the preparation was tried in three patients. A decrease or disappearance of itching, burning and whealing and fading of some of the lesions were found in two cases after the use of reserpine. One patient showed a generalized Herxheimer reaction-like effect which would indicate that there was some type of response to reserpine. It appears inadvisable to give reserpine in as high a dose as 1 mg for more than one week. A dose of 0.25 mg daily seems to be a safe maintenance dose. As a rule, skin testing to inhalants and foods is not worth while (reviewer's note).

A general approach to the study and management of chronic urticaria is described by Eisenberg.[51] Fifty patients were studied from the standpoint of general disease, presence of infection or parasitic infestation. The allergic study included skin tests for inhalants and foods, inquiry into possible drug allergy and evaluation of the emotional profile. Food factors were incriminated in 48 per cent, drugs in 22 per cent, infection in 12 per cent and inhalants in 44 per cent. Emotional problems were thought to be of significance in 64 per cent of patients. Specific allergic elimination of foods and treatment of inhalant allergies resulted in improvement of 72 per cent of the patients. Adjunct treatment included the oral use of Atarax, 10 to 25 mg three to four times daily, in combination with antihistamines and, on occasion, ephedrine. The reviewer's "batting average" with specific desensitization programs in chronic urticaria is very low indeed. Evidence for psychologic aspects of allergy was complied by Arnold.[2] Psychosomatic aspects of eczematous dermatoses, atopic dermatitis and neurodermatitis studied by various workers are briefly mentioned. This pleasant and engaging paper asks us at least to consider the psychologic aspects of allergy in our dealings with patients who have these disorders.

Feinberg and others[55] found that Atarax relieved chronic urticaria and dermographism in the majority of cases, but the agent is less effective in other allergic diseases. Indirect experimental evidence suggests the possibility that there is a mediating mechanism in chronic urticaria in addition to the possible mechanisms on histamine, acetylcholine and serotonin. Fifteen of seventeen patients with chronic urticaria obtained complete relief. The usual dose of hydroxyzine was 10 mg three times a day, but in the absence of significant relief, it was often increased to 25 mg three or four times a day. A minimal maintenance dose was calculated by trial and error thereafter.

Various situations arise in the office of the allergist which require the prompt use of blocking drugs such as epinephrine and antihistamines. Thomas[207] used injectable parabromdylamine (Dimetane) in doses of from 10 to 20 mg intravenously in patients with severe allergic reactions ranging from insect constitutional reactions to drug reactions and in those with severe urticaria and angioneurotic edema. It was the opinion that the drug had a good potential in the symptomatic relief of these acutely-ill patients. Side effects were minimal. Lipman[106] used parabromdylamine maleate (Dimetane) for a number of allergic conditions. He reported that of nine patients with acute urticaria a good clinical response was noted in six, fair in two and poor in one, and in six patients with chronic recurrent urticaria, a good response was obtained in three, fair in two and one patient had a poor response. Lackenbacher[100] used polaramine in either a 2 mg tablet or 6 mg repetab for five patients with urticaria; control of itching was excellent in three, good in one and fair in one.

DRUG ALLERGY

Various aspects of drug reactions are discussed by Rostenberg.[179] Theories of mechanism include (1) enzymatic interference, (2) allergic sensitization, (3) Schwartzman reaction, (4) Herxheimer reaction and (5) ecologic interference. In some instances, reactions to drugs may be explained on the basis of biochemical host deviation (Motulsky, 1957). Idiosyncrasy and intolerance to drugs surely have more scientific explanations. The Schwartzman reaction involves necrosis and tissue vulnerability to proteolytic enzymes. Antigen-antibody reactions may produce similar changes, resulting in widespread vascular damage. Arsphenamine, sulfonamides and modern antituberculosis drugs commonly produce eczematous drug eruptions. The various classes and types of drug eruptions are enumerated. For management the author quotes: "A, E, I, O, U" of drug reaction therapy: A—avoidance; E—elimination; I—immunologic therapy (penicillin 'desensitization'); O—obstructive therapy (adrenalin, antihistamines); U—unguental or topical therapy."

In discussing drug eruptions, Peterkin[145] calls attention to factors other than the antigen-antibody factor which may be found. Aspirin allergy has been noted in father and daughter; a pigmented barbiturate reaction

developed on the site of a healed sebaceous cyst; a fixed drug eruption in one patient appeared at the site of a primrose dermatitis. Purpuric reactions to drugs may follow carbromal and Sedormid. It has been shown that these drugs produce a lytic reaction on platelets, rendering them antigenic. In these patients a patch test with the suspected drug produced a local purpuric reaction. More recently, biochemical and enzyme theories, especially with reference to arsenical dermatitis, have explained certain behaviors of drug eruptions. The development of bullae, for example, due to arsenical vesicants, can be closely simulated by bullous reactions to barbiturates. Many sulfanilamide reactions have the appearance of vitamin deficiencies, for example, pellagra or ariboflavinosis. It is well, therefore, to consider that not all drug eruptions are on a purely allergic basis.

Chloramphenicol.—Chloramphenicol was among the first of the current broad-spectrum antibiotics introduced to modern medicine. Jackson[83] notes that, soon after its introduction, the drug was unequivocably connected with a number of cases of serious and often fatal blood dyscrasias. These reactions, however, have been infrequent and the drug is again enjoying considerable use. Nausea, vomiting and diarrhea have been less frequent than after the oral use of tetracyclines. Glossitis and stomatitis may appear after large doses or long term administration. Blood dyscrasia appears more commonly after multiple, intermittent and prolonged administration than after a single course of the drug. White females are most susceptible.

Chlorpromazine.—Agranulocytosis following the administration of phenothiazine derivatives such as chlorpromazine was studied by Pisciotta and others[147] in sixteen patients. The drugs were given to mental patients in large dosages over long periods of time. An immunologic mechanism is undoubtedly responsible for some types of agranulocytosis. Probably other mechanisms are involved as well. The disorder was usually recognized by the onset of infection. Leuko-agglutination did not occur, and leukolysis was not found. Readministration of these compounds after recovery was possible in some cases. This tends to negate an immunologic mechanism. Steroids given in nine cases suggested that the corticosteroids have no particular value as marrow stimulators when the marrow is depleted of only granulocytes. van Ketel[212] and others reported sensitization to chlorpromazine. The skin lesions are described. The photosensitivity brought on by chlorpromazine is also noted. Lesions resulting from oral administration of chlorpromazine subside when administration of the drug is discontinued, or in some cases, when smaller doses are used. Allergic eczematous contact dermatitis to chlorpromazine, however, is a more persistent problem. Seven of sixty-two members of the nursing staff in a small hospital had contact dermatitis, and in five of these the dermatitis

was caused by chlorpromazine. A concentration of 2 per cent aqueous strength was suggested for proper patch testing. In this small group, cross-sensitivity reactions with phenothiazine, Phenergan, promazine, methylene blue and Pacatal in 0.5 per cent strength gave negative results. Chlorpromazine may produce agranulocytosis, jaundice, dermatitis and other avascular reactions in the skin. Hollister[75] reports allergic reactions to tranquilizing drugs, including the chlorpromazine, reserpine and meprobamate series. Agranulocytosis produced by chlorpromazine is probably on an immunologic basis. There may be cross-sensitization with other members of the phenothiazine derivatives. Very few reports of sensitization to reserpine have appeared. The unique quality of meprobamate sensitivity is demonstrated by symptoms produced often with the initial dose of the drug; these symptoms include fever, skin eruptions and vascular collapse.

Chlorpropamide.—Chlorpropamide is a new hypoglycemic agent for oral administration in diabetes. In a series of fifty patients, toxic side effects occurred in four according to Stewart et al.[199] In a thirty-three-year-old Negro, who had been taking the drug with good effect for one month, an eruption appeared with the features of erythema multiforme and elements of exfoliative dermatitis. Fever and eosinophilia (25 per cent) accompanied the eruption which took three weeks to subside.

Diuril.—Norins[138] reports the occurrence of a drug eruption following the use of chlorothiazide (Diuril) in an eighty-seven-year-old woman. The cutaneous manifestations consisted of numerous tiny petechiae confined to the exposed areas of the body, suggesting photosensitivity. A striking pattern resulted because the eruption affected only the open areas of her shoes, particularly the great toe since she wore open-toe shoes. The eruption subsided within four weeks after use of the drug was discontinued. Rogan[175] reports the occurrence of dermatitis in three women following the ingestion of chlorothiazide (Diuril). The character of the eruption was grossly similiar in most of the women, consisting of brightly erythematous papular eruptions on the trunk and extremities. The eruption subsided in two weeks after use of the drug was discontinued; one patient required triamcinolone for relief. Jaffee and Kierland[84] report the cases of two elderly men in whom purpura and petechiae developed following the use of Diuril. In the first case the eruption occurred within two days after chlorothiazide therapy was resumed. The eruption was petechial in nature and involved both ankles and later the dorsa of the feet and hands and the distal half of both lower legs.

Erythromycin.— Stryker and others[203] used erythromycin to treat various infections in 210 atopic patients, many of whom received more

than one course of erythromycin. No evidence of allergic hypersensitivity was noted in any of these patients. The literature likewise is free from any great evidence of sensitivity to this agent.

Furacin.—Most dermatologists are acquainted with sensitization from Furacin ointment, particularly in patients forty years of age and over, with stasis dermatitis. Weiner and Fixler[219] studied the topical use of Furacin for bacterial dermatitides in the form of a nitrofurazone-soluble dressing, nitrofurazone cream and nitrofurazone solution containing 0.2 per cent of the active agent. A total of 212 dermatologic patients suffering from various pyogenic dermatoses were selected. The clinical results were considered satisfactory in 81.6 per cent, unsatisfactory in 11.3 per cent and equivocal in 7.1 per cent. Hypersensitivity reactions were observed in only 3.3 per cent of the 212 patients. It would seem, therefore, that this preparation is not as sensitizing as previously reported.

Gold.—The question is raised whether an immediate urticarial reaction could develop in a patient who received an initial injection of 25 mg of gold sodium thiomalate.[158] The consultant stated that immediate allergic reactions to the administration of gold, while rare, are not unknown. Probably 10 per cent or less of patients will note an acute exacerbation of rheumatic symptoms within twenty-four to forty-eight hours after intravenous administration of gold and this is generally considered to be an allergic manifestation. This reaction suggests the dose should be decreased.

Iodides.—Cutaneous sensitivity to iodide ingestion is so variable that practically every type of skin lesion has been reported as a sensitivity reaction to iodide. Jones and others[86] present the case of a sixty-seven-year-old-man in whom an unusual morphologic variant developed, manifested by ulcerative and carbuncular lesions due to iodides. Reports have previously appeared in the literature of the successful response of iododermas to corticotropin therapy, and that in an iodide-sensitive person bronchography had been accomplished with an iodine-containing contrast medium by prophylactic administration of corticotropin. In the patient presented, two separate episodes were observed. The healing time of the first episode was thirty-one days without the use of corticotropin, and thirty days for the second episode with the use of corticotropin. The second episode, however, was more extensive than the first.

Kanamycin.—Kanamycin, a new antibiotic, has a structure which closely resembles that of neomycin, according to an editorial.[50] It is poorly absorbed from the gastrointestinal tract. Its action is predominantly bactericidal. It is particularly active against Staphylococcus, E. coli, Aerobacter, Klebsiella, N. gonorrhoeae. Intramuscular doses of 0.25 to 0.5

gm may be given at six to eight hour intervals for most strains. Drug eruptions and drug fever were uncommon, but eosinophilia during the administration of the drug was frequently noted.

Kynex.—In the course of the treatment of dermatitis herpetiformis with sulfamethoxypyridazine (Kynex), Perry and Winkelmann[144] noted a number of adverse reactions. Since Kynex is a member of the sulfonamide family, it is well to review the reactions to this class of drugs: (1) potentially serious reactions, including complications of the urinary tract, sensitization reactions (drug fever, rash and contact reactions), blood dyscrasias, and hepatitis; (2) milder reactions which include acidosis, cyanosis and reactions related to the central and peripheral nervous systems. Of a series of twenty-eight patients with dermatologic conditions who were given Kynex, five showed adverse reactions. In one patient pyrexia, arthralgia and albuminuria developed and these symptoms were interpreted as manifestations of a toxic reaction rather than true hypersensitivity. It is recommended that routine studies of the blood and urine should be made; blood levels of Kynex need to be determined at various intervals if the preparation is to be given over a long period. This paper also notes recent reports of maculopapular eruptions and fever due to Kynex reported by Grieble and Jackson[70] (1958) and severe bullous and other eruptions from Kynex reported by Lindsay and colleagues (1958). Tisdale[208] described focal hepatitis, fever and skin rash following therapy with sulfamethoxypyridazine (Kynex), a long-acting sulfonamide. A sixty-eight-year-old Negro received sulfamethoxypyridazine, 1 gm orally, daily for thirty-seven days as well as nitrofurantoin, 300 mg orally for about two weeks. Prior to this he had received sulfisoxazole (Gantrisin), 4 gm, a day for five days prior to suprapubic prostatectomy. Following the course of sulfamethoxypyridazine, he experienced severe generalized itching associated with the occurrence of a diffuse maculopapular eruption over the trunk, arms and legs. Several days later the urine was recorded as "dark red" and the patient became febrile. Microscopic examination of a liver biopsy specimen revealed a disseminated exudative process. The patient recovered with the use of steroids, chloramphenicol and streptomycin.

Sulfonamides have been associated with a serum sickness-like syndrome characterized by fever, morbilliform or urticarial eruptions, conjunctival (photosensitivity) reactions, bronchospasm and leukopenia. Cross reactions to different sulfonamide preparations may occur. Bell and others[13] report prolonged urticaria after ingestion of sulfamethoxypyridazine (Kynex) in a twenty-nine-year-old physician. This occurred after the ingestion of a single 500 mg tablet, followed by diffuse urticarial wheals and wheezing. Chronic urticaria persisted for seventeen weeks, although the asthmatic symptoms subsided. Of eighty-five patients receiving sulfamethoxypyridazine (Kynex) untoward reactions to the drug developed

in 10 to 12 per cent, according to Lindsay and others.[105] Maculopapular and erythematous dermatitis developed over the trunk in most of the patients. The case history of a sixty-eight-year-old white man is recorded; large bullous and purpuric lesions developed and the patient appeared moribund. He required intravenous corticotropin for recovery. If a cutaneous reaction is to occur, it will appear within one to five days if the patient has taken sulfonamides previously. Otherwise, the average time of onset is fourteen days. In response to a question on severe toxic dermatitis following the use of one of the new long-acting sulfonamides, the consultant[151] stated that erythema after severe drug dermatitis may persist for a long time and represents a local vascular disturbance. The patient was advised to avoid all sulfonamides in the future.

Meprobamate.—Meprobamate hypersensitivity resulting in maculopapular or urticarial cutaneous eruptions or a combination of these has previously been reported. Brachfeld and Bell[27] report the case of a fifty-one-year-old woman who was given 400 mg of meprobamate four times daily because of continued restlessness while in the hospital for a myocardial infarction. In a few days, extensive sloughing ulceration of the mucosa of the inner cheeks, tongue and palate occurred in addition to a troublesome proctitis. Additional questioning revealed that she had a similar episode about a year previously after a single tablet of meprobamate. The patient made rapid recovery on minimal steroid therapy. Clinical manifestations of drug eruptions, especially in hospitalized patients, are becoming more difficult to recognize. This is particularly true of patients receiving multiple antibiotic therapy. Charkes[37] describes a case of meprobamate sensitivity. A total of 113 cases of idiosyncrasy have been reported. The eruption is diffusely erythematous, maculopapular or urticarial and at times combinations of these three elements. Occasionally, vesicular and pustular types have been recognized. Nonthrombocytopenic petechiae have been noted in 16 per cent of cases.

Neomycin.—Calnan and Sarkany[35] found fourteen cases of contact dermatitis from neomycin. As previously reported by Epstein[53] (1958), the sensitivity is not rare and patch tests frequently give negative results. With intradermal tests of high dilutions, the results are alway positive. It was thought by Calnan and Sarkany that the negative patch tests represented a failure of penetration of the allergen. Cross-sensitivity with streptomycin has been seen. In the streptomycin sensitive patients, however, neomycin sensitivity was not found. Associated sensitivity reaction to bacitracin or framycetin was not found. Eczematous sensitization to neomycin and bacitracin was studied by Pirilä and Wallenius.[146] The two drugs were used simultaneously over a twenty-month period in twenty-eight patients. Epicutaneous tests were performed in twenty-five patients with various components of the ointment used. Positive reactions were

obtained in all twenty-five cases to neomycin, and in eighteen to bacitracin. Bacitracin sensitivity is usually a rare finding. It is possible that the neomycin and bacitracin compounds which were used contained a substance that caused sensitization to both. It is to be remembered that Sidi and others[185] reported cross-sensitization between neomycin and streptomycin (1958). The ordinary patch testing was insufficient to elicit a reaction in their cases. Positive results were obtained only after scratching through the epidermis. There was a good deal of talk about neomycin sensitivity at the American Academy of Dermatology in December, 1959. At a round table discussion, some doubted the incidence reported by certain authors. Baer and Witten[6] state that sensitization to neomycin is not particularly common and that cross-sensitization to streptomycin and perhaps also to bacitracin is not uncommon. It is also noted that allergic sensitization sometimes cannot be demonstrated by the conventional patch test and intradermal or intracutaneous tests are positive as a delayed forty-eight-hour reaction. Patch testing over a scratch test is sometimes necessary to show the existence of sensitization. It is also important to remember that neomycin hypersensitivity may be recognized clinically not as an acute vesicular dermatitis but more as a low grade seborrheic or even psoriasiform dermatitis described best as a subacute erythematosquamous or an acute papulovesicular eruption.

Para-aminosalicylate.—Fever and a maculopapular eruption occurred in three of 100 children who were treated at Bellevue Hospital, New York, with PAS for various forms of tuberculosis.[116] Additional symptoms included headache, chills, malaise, anorexia and conjunctivitis. When fever develops between the second and sixth weeks of therapy, such patients should be regarded as suffering from hypersensitivity to PAS. Readministration of analogues of PAS should not be started in less than three weeks.

Penicillin.—The query[163] was raised as to the definite relationship between the total dosage of penicillin and the incidence of reactions to penicillin. The consultant replied that this question cannot be easily answered. About 10 per cent of the population may become sensitive to a food, drug, cosmetic or other substance during their lifetime. Among the 10 per cent there is still a great variation in the resistance to sensitization. Some persons acquire sensitivity after a single contact with penicillin and others require two or more contacts. Some patients have had several hundred injections of penicillin before sensitivity developed. Anaphylactoid reactions have followed skin testing with penicillin, the sucking of a single penicillin troche, or the taking of a single penicillin tablet. Serious reactions have also followed the administration of poliomyelitis vaccine, even though the finished vaccine contains only a minute amount of penicillin (Pelner).[142] In response to a question on the emergency treatment

of anaphylaxis due to penicillin, the consultant[162] stated that the anaphylactic reaction may be recognized by the sudden appearance of generalized urticaria, dizziness, cyanosis, tightness in the chest, circulatory collapse, pulmonary edema, shock and, frequently, death. Emergency treatment includes the administration of oxygen, digitalis, antihistaminics by injection, a 1 to 1000 solution of epinephrine subcutaneously, intravenously, or both, and the intravenous administration of ACTH or hydrocortisone. The prognosis may be grave in severe anaphylactic reactions. Parenteral administration of penicillin may be more serious than oral administration, although deaths have been reported when the latter route was used.

A study of sensitivity to repository penicillins was made by Willcox and Fryers[221] who show an incidence of possible reactions as high as 4.8 per cent of the patients treated. The figure of 0.6 per cent for proven penicillin sensitivity is well below the often quoted American figure. A total of 7300 injections was given to 895 patients over an eleven-year period. No anaphylactoid reactions were observed. Patients who were previously given topical penicillin had a higher incidence of reactions to repository penicillins. Bernstein and Houser[14] were interested in the problem of successful control of epidemics of diseases resulting from Group A streptococci among military personnel, employing penicillin as a prophylactic agent. Two separate pilot studies were made. About 4 per cent of the men had a reaction that could be attributed to penicillin given by intramuscular injection in a dose of 1,200,000 units of benzathine penicillin. Serum sickness, urticaria and pain at the injection site could be attributed to penicillin, but the maculopapular eruptions, arthralgias, pruritus, and fever occurred with equal frequency in the control groups given penicillin and saline. It is suggested that something less than 1,200,000 units be used in mass streptococcal prophylaxis. In 1955, a committee of the American Heart Association endorsed the use of benzathine penicillin G intramuscularly for continuous rheumatic fever prophylaxis, regardless of the patient's age. A long range study of untoward reactions to benzathine penicillin G in a study of rheumatic fever prophylaxis in adults was made by Hsu and Evans.[78] Thirty-two adults with rheumatic heart disease had follow-up studies of from one to twenty-seven months; 18.7 per cent had allergic reactions, including one case of fatal anaphylaxis, two of serum sickness and three of a generalized pruritic eruption. The death reported was that of a fifty-four-year-old woman who had no personal or family history of allergy. She had been given benzathine penicillin prophylaxis beginning in June 1955; death from anaphylaxis occurred in December 1956, within four minutes after an intramuscular injection and in spite of prompt symptomatic treatment.

A twenty-two-year-old white man with severe erythema multiforme (Stevens-Johnson syndrome) is reported by Yaffee.[225] Two weeks before the onset of the first lesions, he suffered an abrasion of the leg which

was treated with penicillin ointment. This was followed by an itching, weeping, vesicular eruption at the site. Since this was regarded as an infection, penicillin was given intramuscularly and ten days after the first injection the ulcerative mucosal picture and severe toxemia characteristic of Stevens-Johnson syndrome developed. He recovered completely after treatment with intravenous corticotropin (ACTH). Dermatitis caused by penicillin in milk and cheese has previously been reported. Vickers and others[213] record the case of a woman of fifty-five years in whom a dermatitis developed from milk showing a penicillin content of only 4 units per cubic centimeter. Desensitization was accomplished by starting with one unit intramuscularly and continuing treatment until a tolerance dose of 1 million units was reached. Cows in which mastitis develops are usually given 100,000 units of procaine penicillin into the infected quarter by dairymen. The Food and Drug Administration in this country has a regulation which states that milk from any cow treated with penicillin should be discarded for seventy-two hours. Warren[217] treated ten cases of allergy to penicillin with Pabalate (a mixture of sodium salicylate, sodium para-aminobenzoate and 50 mg of ascorbic acid). One tablet was given four times a day and symptoms were controlled in twenty-four to forty-eight hours. It is possible that the anti-inflammatory effect of salicylates was responsible for the relief obtained by these patients.

In twenty-five of thirty patients with fatal penicillin reactions, as reported by Rosenthal,[177] the reactions were of the immediate type. In fourteen patients no inquiry was made as to previous administration or reaction to penicillin. Legal action resulted in nine cases, with some out-of-court settlement. Despite a history showing no previous administration of penicillin, it is quite likely that a patient may be sensitized by the drug which is present as a contaminant in milk or cheese. Chemical examination of the viscera and routine autopsy findings in anaphylaxis may be negative as to evident causes of death. Cooper,[40] in commenting on the article by Rosenthal, discusses the point, whether the use of penicillin should be abandoned because of a few tragic mishaps. Cooper points out that well over thirty cases of known deaths due to penicillin have been reported in a period of five years, and probably many more cases have never been reported. He urges extreme caution in patients who, according to their history, are shown to have penicillin hypersensitivity.

Penicillinase.—Friedlaender[61] treated fifty patients with a purified form of penicillinase. These were individuals with penicillin hypersensitivity who rapidly improved after intramuscular administration for serum sickness type reactions, acute urticarial and nonurticarial eruptions and chronic urticaria. Two injections of 800,000 units each at three-day intervals appeared to be the most effective form of treatment. This mode of treatment is not indicated in the management of immediate anaphylactic reactions to

penicillin. In one patient in this series who received penicillinase intravenously a shaking chill and a frightening febrile reaction developed. Previous reports of the use of penicillinase (Neutrapen) in neutralizing the effects of penicillin in patients showing hypersensitivity to this agent indicated that the preparation was essentially nontoxic. The first report concerned fifty-two patients. Hyman[81] reports anaphylactic shock after therapy with penicillinase in a fifty-year-old woman in whom urticaria developed six hours after an injection of 600,000 units of procaine penicillin given intramuscularly. Within two minutes of receiving 800,000 units of penicillinase intragluteally, the patient complained of weakness, dizziness and dimness of vision. She recovered with the intravenous use of epinephrine and further supportive treatment. In this connection, Reisch[170] reported two additional cases of allergic reaction to penicillinase. In one case, a thirty-five-year-old man was given penicillinase intravenously and the same dose of 800,000 units intramuscularly. One hour later he had a severe shaking chill with slight respiratory difficulty and cyanosis. There was soreness at the site of injection accompanied by urticarial lesions. He was given steroid therapy and all lesions began to subside. However, because he continued to show urticaria, another injection of penicillinase, 800,000 units, was given intramuscularly without any febrile reaction. The second patient showed a somewhat similar course with the first injection of penicillinase. Despite this, 800,000 units of penicillinase was given intragluteally ten days later, and he again experienced nausea, chills, fever and lethargy. Becker[10] further discusses allergy to penicillinase. This is a protein and allergic reactions may occur after repeated injections of the enzyme. If repeated injections are given over a short period during treatment of a penicillin reaction, it is thought that antibodies would not have time to develop. If the patient was given a further injection, or injections of the enzyme were given months later, a true allergic reaction might appear. It is stated that within fifteen minutes after an intramuscular injection of penicillinase, no circulating penicillin can be detected, and this would hold for an even shorter period if the enzyme were injected intravenously. It is therefore felt that penicillinase may be lifesaving for a patient who goes into shock and whose condition is temporarily controlled by epinephrine and pressure agents for a number of hours. In two patients with complete anuria for days associated with a penicillin reaction who did not respond to conventional means of treatment, marked diuresis occurred four hours after the injection of penicillinase. Zimmerman[226] was able to prevent penicillin reactions from administration of poliomyelitis vaccine by giving penicillinase at the same time. Penicillin is present in poliomyelitis vaccine in concentrations of 1 to 200 units per cubic centimeter. The author suggests that in patients with known penicillin allergy, penicillin-free vaccine should be used.

Procaine.—Fisher and Strum[58] found that the allergic eczematous sensitivity to procaine may be fairly common in the general population. It is an occupational hazard in the dental profession. Thirty-six patients were found who had strongly positive reactions to patch tests with 2 per cent aqueous solution of procaine hydrochloride. There is cross reactivity in some to paraphenylenediamine, benzocaine and para-aminobenzoic acid. Of twenty patients with allergic eczematous sensitivity to procaine, none showed immediate local wheal reactions to intradermal procaine. None had general urticarial or anaphylactoid reactions. In this group, the patients with allergic eczematous sensitivity to procaine did not show any vascular or anaphylactoid allergy to intradermal tests, subcutaneous injections and ingestion of procaine. Dentists in whom sensitivity to procaine has developed can use Xylocaine without cutaneous reactions. Local allergic edema induced by injected procaine was noted by Siegal[186] who observed three patients demonstrating repeated reactions to procaine. This was manifested by marked swelling of the cheek and face at the site of injection of the drug for dental anesthesia. A twenty-four-hour papule appeared following intradermal injection of procaine. It was thought that slowly absorbed depot penicillin preparations containing 12 per cent procaine in suspension might conceivably be more potent sensitizers than the usual procaine solution. The reviewer notes that there may possibly be some relationship to this type of reaction, to edema seen after an insect bite, and the introduction of other allergens. I do not know of any statistical data on delayed reactions to intradermal testing with insects.

Pronestyl.—Procainamide (Pronestyl) was introduced in 1950 as a treatment for cardiac arrhythmias. It has become widely used because it is effective and relatively nontoxic. Luton[110] describes a febrile reaction in a sixty-one-year-old man who had repeated episodes to procainamide therapy. Patients have previously been described, however, in whom maculopapular pruritic eruptions have developed in addition to febrile episodes. It is to be noted that these cases are rare.

Sandostene.—Three interesting cases of agranulocytosis associated with Sandostene therapy (thenalidine tartrate) are described by Adams and Perry.[1] Two patients died and one recovered. All physicians should be alert to the occurrence of granulocytopenia in any patient with sudden fever, chills or sore throat while a potentially toxic drug is being administered. Apparently antihistamines, including tripelennamine (Pyribenzamine) hydrochloride, have been implicated in depression of bone marrow and agranulocytosis.

Streptomycin.—Fourteen cases of streptomycin dermatitis were seen in the nursing staff of a London hospital over a period of eight years.

Patients were patch tested with a 5 per cent aqueous solution of streptomycin by Wilson.[223] Nursing personnel who have a high degree of sensitivity to streptomycin may never be able to handle the preparation again. Some patients lose their sensitivity with time, but these are the mild cases. Pruritus, erythema, eczema, photosensitivity, urticaria, exfoliative dermatitis and purpura have been reported in patients who have been treated with streptomycin.

Tetracycline.—Dermatitis medicamentosa apparently due to tetracycline is reported by Ziprkowski and Glazer.[227] There are a few reports of hypersensitivity to tetracycline. The case of a thirty-five-year-old nonatopic woman is reported who was treated with penicillin, streptomycin and achromycin for otitis media. Following the administration of two capsules of achromycin of 250 mg a year later, intensive itching and an extensive morbilliform eruption and fever developed on the same day. She responded well to symptomatic treatment including intravenous administration of ACTH. A repeat test was not made. In response to a question on the best treatment of severe rectal itching, diarrhea, and glossitis after prolonged use of antibiotics, the consultant stated that the prolonged use of antibiotics may cause a marked modification of the normal intestinal flora.[149] Gram positive organisms and some gram negative organisms may be suppressed, and this supression may be followed by an overgrowth of fungi, especially Candida. Antibiotics may also act as primary irritants. Steroid ointments will usually control localized anogenital pruritus. Mycostatic preparations are helpful in Candida infections. Acidophilus milk, buttermilk and other foods prone to build up the gram positive flora in the intestine may be useful.

Tolbutamide.—Tolbutamide (Orinase) has by this time achieved widespread use and has a remarkable record of safety. Side reactions have been relatively few. Skin eruptions and mild granulocytopenias as well as mild gastrointestinal disturbances have been reported. Jost[87] records the case of a sixty-nine-year-old man who was admitted to the hospital because of weakness and collapse. He was found to have hypertension and an old history of diabetes. Tolbutamide therapy was started, with control of the diabetes. The patient did not return for follow-up visits and when seen again he showed a severe, protracted and probably lethal aplastic anemia. Although no blood counts were taken before tolbutamide was administered, the patient had looked well for many months. When he was re-hospitalized he had a severe pancytopenia. This was followed by pneumonia from which he apparently was recovering when he suddenly died.

Trilafon.—Perphenazine (Trilafon) therapy in fifty patients with mental disorders requiring long continued tranquilizing programs was studied

by Ayd.[3] Because phenothiazine derivatives have caused agranulocytosis it had been suggested that frequent blood cell counts might serve as adequate warning. However, transient leukopenia is common in patients treated with these drugs and a better index is continued observation for fatigue, weakness, sore throat and any evidence of illness or infection. These symptoms are frequent clinical warnings of beginning agranulocytosis. In this study (nineteen to thirty-four months), no serious side effects were noted.

Vaccine.—Stefanini and others[197] report the occurrence of a generalized severe purpuric eruption in a woman seven days after injection of 2 ml of polyvalent Asiatic influenza vaccine. It was thought that the virus itself was the allergen concerned. Sensitivity studies to egg protein and preservative were negative. Passive transfer of sensitivity was positive. A question[157] was raised regarding reactions after injections of tetanus toxoid in three patients in whom delayed reactions developed between five and ten days after the booster injection. The reaction was characterized by marked local redness, swelling and itching, with regional lymphadenopathy and in one patient, at least, fever and polyarthritis. The consultant stated that in the early days of tetanus toxoid prophylaxis, allergic reactions of variable degree of the serum sickness type were encountered. It was suggested that sensitivity tests be conducted with the various materials (obtained from the manufacturer) that go into the tetanus toxoid. Changing to a preparation made by another company was also suggested.

STEROID HORMONES

The effectiveness of topically applied hydrocortisone preparations for inflammatory eczematous dermatoses has been well established. Studies have previously demonstrated that hydrocortisone penetrates both normal and abnormal skin sites in man. The subsequent fate of this compound following percutaneous absorption was studied by Malkinson and others.[112] *In vitro* incubations of fresh human skin slices with cortisone and hydrocortisone in phosphate Ringer's buffer solution were used. This was followed by extraction of steroid substances and the separation of these compounds by paper chromatography. Hydrocortisone (free alcohol) and cortisone (free alcohol) are actively metabolized chiefly by the corium in the skin. The metabolic product of hydrocortisone detectable by these techniques possesses the characteristics of cortisone. The metabolic product of cortisone possesses the characteristics of hydrocortisone. The metabolic alteration of cortisone occurs more rapidly than that of hydrocortisone. The striking differences between the anti-inflammatory effects of topical hydrocortisone and cortisone remain unexplained. It is possible that the increased anti-inflammatory potency of prednisone and prednisolone in human beings may be related to the much slower metabolism of

these compounds in body tissues when contrasted with the metabolic turnover in cortisone and hydrocortisone.

Schamberg and others[182] studied the effect of steroid lotions on inflammatory dermatoses by the double-blind paired-comparison method which allowed for the analysis of results by biostatistical methods. Patients with eczematous eruptions were randomly selected and nine dermatologists used coded, paired vials in this study; 510 patients participated. Fludrocortisone lotion was compared with a simple control lotion base in 177 patients. No statistically significant differences in effect could be demonstrated in this group of patients. Further, no significant difference was found between the effect of a 0.1 per cent fludrocortisone lotion and 1.0 per cent hydrocortisone lotion in 217 patients, or between 1.0 per cent prednisolone lotion and 1.0 per cent hydrocortisone lotion in 116 patients. It was thought that the placebo reactor is an important potential source of error in studies of the effect of therapeutic agents. The limitations of the study are discussed.

Triamcinolone was used by Kanof and others[90] in seventy-five patients with various dermatoses. Fifty-eight took the drug without interruption for three to sixteen months. The drug was used in the following conditions: atopic dermatitis, thirty-seven patients; contact dermatitis, eleven; psoriasis, five; seborrheic dermatitis, two; exfoliative dermatitis, three; nummular eczema, three; alopecia areata, two; lichen planus, one; pemphigus erythematodes, two; dermatitis herpetiformis, four; toxicoderma, two; infectious eczematous dermatitis, two, and urticaria, one. Many other investigators have reported similar experiences, namely, that triamcinolone has marked anti-inflammatory and antipruritic effects in many dermatoses. The side effects were as follows: moon facies, eight; acneiform eruptions, eight; stomach pain, three; nausea, three; hypertrichosis, three; severe perspiration, two; glycosuria, one; vomiting, one; headaches, one; vertigo, one; mental depression, one; stomach ulcer, one, and celluititis, one. In only two instances were the side effects sufficient to discontinue triamcinolone. Smith and others[192] found that triamcinolone acetonide was a highly effective new topical steroid. By a double-blind symmetrical paired comparison study 0.1 per cent triamcinolone acetonide was compared with 1 per cent hydrocortisone topically in lotion, cream and ointment bases in a series of 109 patients. Triamcinolone was found to be superior to 1 per cent hydrocortisone. Sternberg and others[198] reported that improvement was obtained in fourteen of fifteen cases of atopic dermatitis with topical trimacinolone acetonide and eight of eleven cases of contact dermatitis. Smith and others[191] studied the effect of triamcinolone acetonide as a topical therapeutic agent in 129 patients using 0.1 per cent strength in lotion, cream and ointment bases and this was compared to 1 per cent hydrocortisone in similar bases. Triamcinolone was found to be more efficacious than hydrocortisone in certain cases. In no

instance of atopic dermatitis was hydrocortisone considered to be better than its physical homologue containing triamcinolone acetonide. Montgomery[124] found that Kenalog-Spectrocin-Micostatin ointment was the most effective medication yet employed in the treatment of cutaneous moniliasis. Dameshek and Rubio[43] discuss the steroid treatment of idiopathic thrombocytopenic purpura with specific reference to the use of triamcinolone. Also included were auto-immune hemolytic anemia and leukemia in sixteen consecutive patients. Muscle weakness, hypopotassemia, bleeding peptic ulcer, severe staphylococcic infection, cardiac failure and other minor reactions were noted in a small percentage of the patients treated. It was thought that this drug should be studied further before it is used in the relatively large doses often required in this group of disorders.

It is well known that the lives of patients with systemic lupus erythematosus may be prolonged by the use of steroids early in the disease. Dubois[47] treated twenty-nine patients with systemic lupus erythematosus with triamcinolone. This hormone is 1.3 times as powerful as prednisone and 4.4 times as potent as hydrocortisone as an anti-inflammatory agent. Symptoms improved and evidence by clinical and laboratory tests gradually subsided, except for long-standing renal involvement. Cushingoid facies, hirsuitism and striae were more commonly found than with the steroids formerly used. The most distressing side effect was muscle weakness, which occurred in six patients from four to thirty-two weeks after the onset of triamcinolone therapy. The loading dose of triamcinolone was individualized; patients in whom the disease was poorly controlled with other types of management were given 40 mg per day. The dosage was gradually reduced after the clinical and laboratory findings improved.

Lerner[103] showed by double-blind study involving thirty patients with various dermatoses, such as hand eczema, atopic dermatitis, nummular eczema, lichen simplex, and so forth, that both 0.1 per cent triamcinolone acetonide (Kenalog) and 1 per cent hydrocortisone in cream, lotion and ointment formulations were effective but that most patients preferred triamcinolone acetonide. Triamcinolone (Aristocort) was used by Kanee[89] in thirteen patients with selected dermatoses. Patients with systemic lupus erythematosus may improve when they are transferred from one steroid to another. In one patient with this disorder, general improvement was noted when treatment was changed from prednisone to triamcinolone. Improvement could be continued with a maintenance dose of 14 mg of triamcinolone. Crowe and others[41] used triamcinolone acetonide in the treatment of a number of skin diseases. Triamcinolone is said to have twenty times the anti-inflammatory activity of hydrocortisone. In spite of this, twenty patients with atopic dermatitis in this study preferred triamcinolone over hydrocortisone and twenty patients found hydrocortisone equally effective. Double-blind studies indicated significant differences between triamcinolone and hydrocortisone, and triamcinolone was preferred to hydrocortisone. Kalz[88] investigated the effect of triamcinolone

and 6-methylprednisolone on forty-eight patients, including twenty-four with severe atopic dermatitis. Satisfactory improvement was obtained in twenty-one of twenty-four patients with atopic dermatitis by the systemic administration of 20 mg of these agents daily for two to five days and prompt reduction in dosage until the minimal effective dose was reached. These agents as less likely to have electrolytic effects. The reviewer notes, however, that there has been much difficulty with these agents, particularly with triamcinolone, in interference with protein synthesis and resultant loss of muscle mass in some patients. Robinson[173] describes the anti-inflammatory action of 0.1 per cent triamcinolone acetonide lotion. It is found to be similar in action to that of lotions containing 0.1 per cent fludrocortisone or 1 per cent hydrocortisone. A number of itching dermatoses were benefited. There were no significant effects on psoriatic lesions.

Medrol (6-methylprednisolone) was used in the treatment of fourteen patients with chronic widespread dermatoses who had required continual therapy with other steroids for a period of over two years before this agent was used. Dwyer[49] states that these included three cases of pemphigus; one severe generalized bullous dermatitis herpetiformis; four widespread severe nummular eczemas; four severe exudative atopic dermatitis, and two cases of extensive lichenoid neurodermatitis. In these cases the Medrol requirement was slightly under 65 per cent of the maintenance dose of prednisolone. The incidence of deleterious side effects was greatly reduced with Medrol. Goldberg[67] used 6-methylprednisolone for a group of 201 patients with seventeen different dermatologic problems. The average loading dose was 8 to 12 mg daily and treatment was continued for ten or more days after the patient was well. Patients who had dermatoses with allergic backgrounds responded best to Medrol. However, patients with atopic dermatitis gave equivocal responses. Three patients with bullous erythema multiforme who had failed to respond to various antibiotics and steroids, including intravenous ACTH, showed an excellent response to 6-methylprednisolone and were discharged from the hospital within ten days of the onset of treatment with this agent. Sixty-seven patients and ten healthy volunteers were treated with Medrol to observe its effects and side effects.[120] Ten cases of disseminated lupus erythematosus were included in this group. Forty subjects showed disturbances of body weight, acne was seen in nine and mental changes in eight. As is usual with most other steroids, attempts to avoid unpleasant side effects by reducing the dosage led to the prompt return of the original symptoms. Methylprednisolone has a stronger anti-inflammatory effect than prednisone and prednisolone, but each case must be carefully evaluated. The subjects were observed for periods up to seven months.

Dexamethasone (Decadron) was used by Kohn and Grater[99] in 240 patients suffering from various allergic disorders. Oral dexamethasone was given in dosages comparable to those of other steroids. The prepara-

tion is presently available in 0.75 mg and 0.5 mg tablets. Length of treatment in this group varied from five days to seven months. Six patients with atopic dermatitis showed satisfactory results; in three patients urticaria was controlled, and in one patient it was not controlled. It is the opinion that dexamethasone is one of the most potent available steroids. The most commonly observed side reactions were mental stimulation, increased appetite and epigastric distress.

An excellent survey of the topical and systemic use of corticosteroids in the treatment of skin disease has been recorded by Sulzberger, Witten and Kopf.[205] This includes a very useful table of most of the proprietary corticosteroid preparations which are currently available for topical use. Useful tables of dermatoses benefited by the topical application of corticosteroids as well as tables of indications for systemic corticosteroid therapy are given. The major and minor complications of systemic corticosteroid therapy are tabulated. In general, the material is noncontroversial and most dermatologists would agree with the use of systemic corticosteroids in very severe and refractory cases of eczematous contact dermatitis, atopic dermatitis, exfoliative erythrodermas, nummular eczema and eczematous or pustular eruptions of the hands. Other diseases mentioned, such as pemphigus, systemic lupus erythematosus and dermatomyositis, are usually managed by the full-time dermatologist. In the reviewer's experience, systemic corticosteroid therapy is less helpful in cases of acute urticaria and angioedema, although one is often forced to use these agents when epinephrine and intravenous antihistaminics are not effective. Probably intravenous Medrol in 20 to 40 mg doses would be helpful since it is a short-acting corticosteroid and reports, at least up to this time, indicate that there are few side effects from the reasonably long-continued administration of this preparation.

Transfusion reactions are of four types: pyrogenic, manifested by fever, chills, nausea, vomiting and headaches; allergic, manifested by urticaria and sometimes wheezing; reaction to the plasma of the blood, manifested by chills, fever and muscular pains, and finally the dreaded hemolytic reaction which sometimes can be fatal. Spellman[196] reports a case of transfusion reaction in which ACTH and cortisone successfully blocked the hemolysis expected from an incompatible blood transfusion. Two patients with systemic lupus erythematosus responded to chloramphenicol therapy, according to Wells.[220] Later, when L. E. cells were found, a rapid response to prednisolone therapy was noted.

Stritzler[202] presented the case of a forty-year-old woman with atopic dermatitis who had been on intermittent therapy with prednisone and ACTH gel for three years. Generalized itching, swelling of the lids and lips and difficulty in breathing developed following the intramuscular injection of 40 units of ACTH gel. About five months later a test dose of 4 units of ACTH was given and this was followed by generalized itching and urticaria. Passive transfer tests were positive. Scratch tests were

positive to beef and pork ACTH but negative to gelatine and to beef and pork antigen. It was suggested in the discussion that the patient was probably allergic to ACTH which is a polypeptide.

An extensive case of erythema multiforme (Stevens-Johnson syndrome) with dermatitis exfoliativa is recorded by Goldman and Goldman[68] in a nineteen-year-old white woman. No specific etiology was determined and the patient recovered with the intravenous use of corticotropin and corticosteroid therapy along with symptomatic treatment and antibiotics. In spite of this, an ulcerative keratitis and a corneal ulcer of the left eye developed. Isolation of the virus of herpes simplex from the vesicular fluid in a patient with erythema multiforme exudativum is described by Foerster and Scott.[59] At present, no single etiologic agent has been found in all cases. Some have incriminated food allergy, drug hypersensitivity, especially aspirin, barbiturates and sulfonamides, toxin-producing bacteria and viruses. The sixteen-year-old girl reported was treated with 40 mg of prednisone daily, with a gradual reduction of dosage as her course improved. The conjunctivitis was treated with prednisone ophthalmic ointment with good results. The reviewer notes that perforation of the cornea has been observed in herpetic lesions of the eye in patients who have been treated with topical steroids.

(To be concluded in the April issue. References will appear with the second installment.)

DARWIN'S IMPORTANCE

We often confuse three criteria in estimating the importance of the great figures in the history of thought. The first is the indispensability of what they wrote or said, regardless of its effect, judged as a stage in the development of our present beliefs. From this point of view, to earn a place in history, a man need only be the first to discover the material or express the idea in question. The second criterion is their effect on other thinkers, and nonthinkers, which, unlike the first, requires publication and recognition (or misinterpretation). The third criterion is the extent of their personal indispensability. To judge this, we must make some estimate of the time that would have elapsed before the same contribution would have been made by others, had the individual under assessment never existed. If we introduce an index of "lucky fame" as the ratio of a man's importance on the second criterion to this importance on the third, it seems very likely that Darwin has the highest index of lucky fame in history.—MICHAEL SCRIVEN. "Explanation and Prediction in Evolutionary Theory," *Science*, 130:477 (Aug. 28) 1959.

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In Memoriam

ARTHUR F. COCA, M.D., F.A.C.A.

Before the year 1959 came to its end, the fields of biology and medicine suffered a severe loss by the death of Arthur Fernandez-Coca, who died on December 11. He was one of the few investigators whose activities linked the "heroic" age of immunology of the past to the present.

Arthur F. Coca was born in Philadelphia on March 20, 1875. He was the son of a distinguished pianist of Spanish origin and mother of Quaker stock. He went to Haverford College where he majored in chemistry. His interests and abilities were wide in range, but he was interested chiefly in biology.

At one time he thought to follow his father's example and become a professional musician, and in fact his talents in music were such that he earned much of his tuition for medical school by playing the organ and by being the choir master. He also excelled in sports, as shown by the fact that he was sent to Oxford, England, to represent his school both in cricket and in long distance running.

He earned his Bachelor of Arts degree from Haverford in 1896 and his Masters in 1899. He obtained his M.D. degree in 1900 from the Medical School of the University of Pennsylvania.

He had attracted the attention of Simon Flexner, who offered him an instructorship in pathology at the University of Pennsylvania. This position he retained until 1905. Feeling the need for further training and wider horizons, he went to Germany. At Heidelberg he did graduate work under Kossel. In 1907, he became assistant to V. Dungern at the Institute fuer Experimentelle Krebsforschung where he stayed until 1909. The experiences of these years decisively influenced his life.

He learned to master the experimental methods which then were just being developed, particularly in the field of immunology. Lifelong friendships were then initiated with his teacher, V. Dungern, with Landsteiner and Hirszfeld. He knew Ehrlich and Warburg well. Their example of critical analysis, of painstaking work and selfless devotion, brought to maturation Coca's innate abilities and inclinations. They blended to perfection with the traditions of his Quaker upbringing.

A further opportunity to widen his experience and to foster independent intellectual growth came in the form of an appointment as bacteriologist to the Bureau of Science in Manila, Phillipine Islands during the years of 1909 and 1910.

When he returned to the United States, he joined Ewing's department at Cornell University, College of Medicine. Beginning as an instructor in pathology and bacteriology, he rose through the ranks, and by 1919 had become full professor of immunology. Here he remained until 1932. From 1928 to 1935, he was the director of the first public organization of its type, the Blood Transfusion Association of New York. He also held an appointment as clinical professor of medicine at the New York Postgraduate School (Columbia University) from 1931 to 1935.

When almost sixty years of age, he began a new career by accepting the position of Medical Director of the Lederle Laboratories. His chief interest was the production and standardization of reliable antigens for both the diagnosis and the treatment of allergic disorders. When in 1949 he retired at the age of seventy-four, he returned to private practice, which he continued until close to the end of his life.

The routine work of the positions he held would have been enough to keep an ordinary man busy. For Arthur Coca, they represented only the framework for his essential activities. His interests ranged far. First of all, there was the scientific work. It enriched nearly every field where immunological procedure can make a contribution to medicine.

A review of Arthur F. Coca's scientific production would exceed the space available. It will be listed in the biography which is now being prepared by loving hands. Only a few examples can be mentioned here, chosen because they may serve to illuminate the working of his mind. He could discern simple, but important, technical needs and devise the means of solving the problems involved. For example, he recommended the use of phenolized saline—still known as "Coca's solution"—for the preparation of antigenic extracts. But he could analyze as well the most complex problems and devise the suitable experimental approach as to their solution. An example of this was his discovery of the third component of complement. One of the major problems in which he did pioneer work was that of the immunological response to malignant growth. As early as 1909, he tried to immunize patients with extracts of their own tumors, an approach which is again being intensively studied at the present time. He was among the first to perceive the need for reliable supply of blood for transfusion and created the prototype of the organization to satisfy the need.

During the years in New York, much of his work was focused on the various aspects of hypersensitivity, both on anaphylaxis in animals and on human allergy. Many important data were collected. The results and the impact of Coca's mind and personality upon his colleagues and co-workers deeply influenced the thinking of this period on the phenomena of hypersensitivity and particularly human allergic disease. The term "atopy," coined by Coca, with all his connotations, vividly exemplifies this influence.

His papers, nearly 200 in number, were masterpieces of presentation. He had the rare ability of writing both simply and precisely and with grace. Of his books, an outline of medical immunology (*Essentials of Immunology for Medical Students,* 1925) was the earliest. In 1931, he produced (together with M. Walzer and A. Thommen) a treatise, "Asthma and Hay Fever in Theory and Practice." It became a classic, and can now be read with profit. In recent years, he presented his observations and views on non-reaginic allergy in a monograph for the medical profession *(Familial, Non-Reaginic Allergy)* and in an outline for the educated layman *(The Pulse Test in Allergy).* Both of these works went through several editions.

Perhaps as much as by his own writing, the development of immunology and clinical allergy was furthered by Coca's editorial activities. He was the founder (in 1916) and, until 1949, the editor-in-chief of the *Journal of Immunology,* until recently the only periodical in this field in the English language. Biology and medicine are deeply indebted to Arthur F. Coca for thus providing and maintaining at high standards an outlet for the publication of the ever more variegated studies of immunology. His scrupulous attention to every detail in content and form of the papers, and the ensuing correspondence imposed a considerable burden, but it was truly a labor of love, from which he derived great satisfaction.

He also served for many years as the treasurer and secretary of the American Association of Immunologists. In this position also, he made an important contribution to the development of the discipline in his self-effacing way, modest, kindly, and yet determined as to what was the right thing to be done.

This determination was a most important trait of Coca's personality. It was characteristically involved in the last major turning point of his career, namely, the decision to go into private practice after he had disposed of all other responsibilities. Years before, Coca had observed that the ingestion of some foods had caused an acceleration of his wife's pulse rate. Avoidance of these same foods had alleviated certain symptoms suspected to be allergic in nature. A few similar cases were studied where clinical relief also was obtained. The circle of investigation widened progressively. When the time of retirement from other duties came, Coca obeyed the voice of his conscience which told him that the further pursuit of these studies was a duty overriding his desire for rest. The results of this work were reported

in a number of papers and the two books mentioned above. The medical profession at large has taken little notice of this work. An objective re-evaluation of these findings is overdue, for observations of such possible impact on the practice of medicine should not be left *in limbo*.

When a number of allergists banded together to form a new organization under the name of The American College of Allergists, Fred Wittich succeeded in enlisting Coca's active interest. He knew full well that no better advice could be obtained in putting into actual form the scientific activities concerned in the new venture. Here, once more, Coca rendered yeoman service without fanfare and fuss. This College will not forget its indebtedness.

Coca was married twice. He is survived by his second wife, Ella Foster Grove, a first-rate immunologist in her own right. Theirs was a most happy union.

To Mrs. Coca and other members of their family, the College extends its heartfelt condolences.—*A.J.W.*

LORAINE ORR DUTTON, M.D., F.A.C.A.

Dr. Loraine Orr Dutton of El Paso, Texas, died January 23, 1960, after a long illness.

Dr. Dutton was born in Waco, Texas, August 2, 1898. He received his A.B. degree from Texas Christian University in 1917, following which he served in the United States Army in Siberia. He was a teaching Fellow of Bacteriology at the University of California from 1919 to 1920 after which he became Instructor of Bacteriology at Texas Christian University where he received his M.S. degree in 1921. He was assistant director of laboratories at Baptist Memorial Hospital in Memphis, Tennessee, from 1921 to 1924, and director of laboratories at Methodist Memorial Hospital in Memphis, Tennessee, from 1924 to 1929. He received his M.D. degree from the University of Tennessee in 1931 and entered practice in El Paso.

Dr. Dutton was a Charter Member of the College and served on the Board of Regents from 1946 to 1949, and for several years served on the Aero-Biology committee. He was a Fellow of the American Academy of Allergy (1939). Membership in other societies included: Academy of Internal Medicine, American Association for the Advancement of Science, Texas Society of Pathologists, American Association of Blood Banks, South Central Association of Blood Banks, and the Association of Allergists for Mycological Investigations, Inc. He was on the staff of Providence Memorial Hospital and R. E. Thomason General Hospital at each of which institutions he was director of laboratories, and Hotel Dieu. He was the medical director of Southwest Blood Bank of El Paso.

Dr. Dutton is survived by his wife, Mrs. Evelyn Dutton, two daughters, Mrs. Harry Hitt and Mrs. William Ramsey, and a son, Robert A. Dutton.—*H.E.P.*

HYMAN FOGELMAN, M.D., F.A.C.A.

Dr. Fogelman was a most loyal worker in the Allergy Clinic at Mt. Sinai Hospital in New York City. He had a keen interest in research, a warm feeling for the patient and his problems, as well as an intense need to serve the community.

We mourn his loss with his family.

Hyman Fogelman became a member of The American College of Allergists in 1954.

HAROLD ABRAMSON

LESTER C. TODD, M.D., F.A.C.A.

Lester C. Todd died on December 29, 1959, at the age of seventy-one.

He is survived by his wife, Mrs. Alice Schlickenmeyer Todd, a son, Lester C. Todd, Jr., and two grandchildren.

Following his public education, he received an A.B. degree from Tabor College. He taught for two years as a supervisor of twenty-five government schools in the Philippine Islands before entering the University of Michigan Medical School, where he received his M.D. degree in 1918.

On graduation, he entered the U. S. Navy Medical Corps and served until the end of World War I, when he was discharged with the rank of Captain.

From military service, he came to Charlotte, North Carolina, where he joined the Crowell Clinic and was in charge of all laboratory and pathology services. He also served as pathologist to the Charlotte Sanatorium for several years.

He was a member of his county, district and state medical societies, the American Medical Association, American Academy of Allergy, South Eastern Allergy Association, American Society of Clinical Pathologists, Southern Medical Association, and Tri-State Medical Association.

Lester Todd's quiet, sincere personality will linger with his colleagues and many close friends as a delightful memory.

He was promoted to Fellowship in The American College of Allergists in 1946.

FRED E. MOTLEY, M.D.
ANDREW D. TAYLOR, M.D.
JOSEPH A. ELLIOTT, M.D.

JONATHAN ZONIS, M.D., F.A.C.A.

Dr. Jonathan Zonis of Boston, Massachusetts, died on July 18, 1959, at the age of sixty.

Doctor Zonis received his medical degree from Tufts Medical School in 1924, and was associated with the Beth Israel and Jewish Memorial Hospitals.

He was a member of the Norfolk County Medical Society, Massachusetts Medical Society, American Academy of Allergy, and The American College of Allergists. Allergists.

He was promoted to Fellowship in the College in 1950.

News Items

ALLERGY SOCIETY OF THE DISTRICT OF COLUMBIA

Officers of the Allergy Society of the District of Columbia for the year 1960-1961 are as follows:

President.....William A. Howard
Vice President.....Harry A. Hortsmann
Secretary-Treasurer.....Audrey M. Connor

LOS ANGELES SOCIETY OF ALLERGY

Officers of the Los Angeles Society of Allergy for the year 1960-1961 are as follows:

President.....Isadore Pietsky
Vice President.....Catherine G. Pearson
Secretary-Treasurer.....Sheldon C. Siegel

Books of Interest

AN INTRODUCTION OF CHILD PSYCHIATRY. Stella Chess, M.D. 253 pages. Grune & Stratton, 1959. Price: $5.25.

A competent primer on modern child psychiatry written by one of the outstanding child psychiatrists, is aimed at the general practitioner, pediatrician, or medical student. Adequately comprehensive, the book includes clinical illustrations. It is not intended to teach psychotherapeutic management.

CURRENT MEDICAL REFERENCES. Ed. by Paul J. Sanazaro, M.D. 535 pages. Lange, 1959. Price: $3.50.

A new book offers convenient starting points for bibliographic investigation of all medical disorders. The enthusiastic endorsements of students, practicing physicians, and medical faculties are anticipated. Selected and annotated references are compiled by authorities, using the journal and textbook literature of the past twenty years and citing "classical" articles as far back as 1912. A careful attempt has been made to select references which are available in the average modern hospital library or through the now widespread interlibrary loan services. The editor is Associate Professor of Medicine, University of California.

MECHANISMS OF HYPERSENSITIVITY. Ed. by Joseph H. Shaffer, M.D., Gerald A. LoGrippo, M.D., and Merrill W. Chase. 754 pages; illustrated. Little, Brown, 1959. Price: $18.50.

In this important book, sixty-five specialists from all parts of the world, working in the fields of allergy, dermatology, immunology, and allied sciences, present their latest findings on immunologic processes as they pertain to problems of hypersensitivity.

CLINICAL EVALUATION OF NEW DRUGS. Ed. by S. O. Waife, M.D., and Alvin P. Shapiro, M.D. 223 pages. Hoeber, 1959. Price: $7.50.

Fourteen authors active in both research and teaching present the methods and standards for the evaluation of new therapeutic agents. They discuss the steps leading from the inception of a drug to its clinical application and offer standards against which the practitioner can critically judge how thorough a new agent has been studied. The editors are from the University of Pittsburgh, and University of Oklahoma.

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